Essentials of Oral Medicine

VISIT…

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Essentials of Oral Medicine

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JAYPEE BROTHERS MEDICAL PUBLISHERS (P) LTD.

• New Delhi • Ahmedabad • Bengaluru • Chennai • Hyderabad
Kochi • Kolkata • Lucknow • Mumbai • Nagpur

Published by

Jitendar P Vij
Jaypee Brothers Medical Publishers (P) Ltd
B-3 EMCA House, 23/23B Ansari Road, Daryaganj
New Delhi 110 002, India
Phones: +91-11-23272143, +91-11-23272703, +91-11-23282021, +91-11-23245672, Rel: 32558559
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First Edition: **2008**

ISBN 978-81-8448-212-6

Typeset at JPBMP typesetting unit

Printed at Rajkamal Press

Dedicated to

My parents, who taught me that the only
way to get anywhere in life is to work hard
and
my wife and son, who bring so much joy to my life
Thank you for being there

Foreword

It gives me great pleasure to write the foreword for this book *Essentials of Oral Medicine*. The book consists of systematic rendering of the subject with a whole chapter on "Ill Effects of Tobacco, Areca Nut and Alcohol." It is well-illustrated with appropriate clinical pictures and provides students with a clear understanding of this science. The design and presentation of this book bears testimony to the meticulous and tireless effort put in by the author, who is a good academician and an excellent teacher. I am sure this book will be well-appreciated and accepted by the dental profession. I congratulate Dr. Gautam Srivastava for his excellent academic venture and wish him all success in his endeavors.

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Preface

This book is primarily intended for undergraduate students. However, students pursuing postgraduation will find this book equally useful. The book contains twelve chapters, which reflect basic as well as applied aspects with emphasis on current developments in oral medicine. The organization of each chapter follows a logical sequence and is supported by high quality colored diagrams and photographs to enable the student comprehend the subject fully and logically. A list of important references covering all chapters is provided for the benefit of those interested in to have detail information. The entire text has been word processed, which greatly facilitated editing and updating the various chapters repeatedly as and when recent literature and reviews became available. I would be most grateful to my readers both teachers and students for their constructive criticism of the book.

Gautam Srivastava

Acknowledgements

The publication of this book would not have been possible without the efforts and cooperation of many people. Firstly, my special thanks to my father Prof Bir Bahadur, who read the proof and offered many marvelous suggestions and criticisms. I owe gratitude to my wife Shalini for her excellent job in designing and drawing the figures, which made the book attractive. I would like to thank my teachers Dr P Sudha, Dr R Heera, Dr VV Kamath, Dr DN Bailoor, Dr Bharat M Mody and Dr R Gopa Kumar for their valuable guidance during my graduation and postgraduation. I wish to express my thanks to my colleagues Dr NDVN Shyam for his valuable suggestions. I acknowledge the cooperation of my students who judiciously read the proof and offered valuable suggestions. I am grateful to my students who acted as models for the photographs of various procedures. I wish to thank Shri JP Vij, Chairman and Managing Director of M/s Jaypee Brothers Medical Publishers (P) Ltd for giving me the opportunity to author this book. I also acknowledge the support I received from Mr Nikhil Bardhan, Asst Incharge, Hyderabad branch. The library facilities of College of Dental Surgery, Mangalore and Manipal, AB Shetty Memorial Institute of Dental Sciences, Mangalore and Govt Dental College and Hospital, Vijayawada are colossally recognized. Finally, I wish to thank my mother Dr Vijaya Devi Mathur for her constant help, not only during the writing of this book throughout my dental education.

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Chapter 1

Dental Recordkeeping

INTRODUCTION

Patient records must provide an accurate picture of the condition / or conditions present on initial examination as well as the clinical diagnosis, treatment options, the proposed and accepted treatment plan, a record of the treatment performed, details about any referrals, and the prognosis and/or outcome of the treatment where applicable.

Recordkeeping Principles

In keeping and maintaining acceptable patient records, a careful practitioner should adhere to the following basic principles:

1. All entries should be recorded in ink, typewritten or be in an acceptable electronic format
2. All entries should be accurate and clean
3. All entries should be signed, initialed or otherwise credited to treating clinician
4. All entries should be dated and entered at time of patient visit in chronological order (late entries should be identified as such)
5. Radiographs and other diagnostic aids, such as study models, should be properly labeled, dated and the interpretation of the findings documented when considered appropriate by the practitioner
6. All items and/or pages properly identified by patient name
7. Adequate recording of patient information, medical/dental history, clinical and radiographic findings, diagnosis and treatment including fees charged, and referrals
8. Responsibility for record completion remains with practitioner providing services

Patient Consent

Following is a list of situations where the patients signature is desirable to see to it that the records are closest to accuracy:

1. Medical history including date
2. Consent for treatment including associated fees
3. Presurgical and postsurgical instructions for major procedures or those done under sedation or general anesthetic
4. Consent for sedation and general anesthesia
5. Financial arrangements
6. Consent to obtain and/or release information
   a. Personal use
   b. To transfer records to another dentist
   c. To transfer records to physician
   d. To transfer records to alternate physician
   e. For referrals
   f. Legal use (lawsuit)
   g. Third party (coroner *(forensic odontologist)*, law enforcement agencies, third party payment)

7. When patients refuse radiographs, treatment or referral to another practitioner

PATIENT RECORD

The extent of the detail required for each individual dental record will vary from patient to patient. It will also depend on the conditions with which the patient presents, and the complexity of the treatment that is required. Certain baseline data, however, should be common to all dental patients. This information includes:

1. Demographic data
2. Financial information
3. Dental history
4. Medical history
5. Clinical examination
6. Diagnosis and treatment plan
7. Referrals and consultations
8. Follow-up notes
9. Emergency treatment record
10. Laboratory record
11. Drugs record
12. Financial record
13. Confidentiality

Demographic Data

The following general information should be obtained from every patient at the initial appointment and updated at regular intervals:

1. Name
2. Age
3. Sex
4. Date of birth
5. Address
6. Telephone numbers (residence and office)
7. E-mail ID
8. Occupation
9. Name and address of any referring health professional, if applicable
10. Name, address and phone number of patients primary physician, if obtainable
11. Name, address and phone number of patients medical specialist (s), if obtainable
12. Emergency contact name and telephone number
13. Previous dentist
14. For minors, name of parent or legally authorized representative

Financial Information

1. Name of the person or agency responsible for payment
2. Insurance information, if applicable

Dental History

The dental history should contain information of personal dental health and previous dental care. Information obtained regarding a patients dental history can supplement the clinical examination, and assists in the planning dental care that is necessary and suited to improve the patients dental health status. The dental history should address the following:

1. Chief complaint (painful tooth/teeth, bleeding gums, crooked teeth, hole in tooth, bad breath, discoloration of teeth, loose tooth/teeth, teeth set, sores, growth, white patch, burning sensation, etc)
2. History of present illness
   a. Origin: When did the problem start?
   b. Duration: Since how long has the problem been present?
   c. Progress: How is the problem progressing e.g., getting better, getting worse or remaining static?
   d. Aggravating and relieving factors: Any factors that aggravate the problem or any factors that relieve the problem?
   e. Radiation: Is the problem radiating e.g., refered pain?
3. Previous dental care (scaling, restoration, extraction, denture, root canal therapy, radiographs, etc)

4. Date of last dental visit
5. Emotional concerns (fear, pain, time, money, embarrassment)
6. Oral hygiene habits
   a. Brushing with toothpaste and toothbrush (frequency)
   b. Brushing with toothpowder and toothbrush (frequency)
   c. Flossing (frequency)
   d. Interproximal brush (frequency)
   e. Others (finger, salt, charcoal, brick powder, chewing neem sticks etc)
7. Oral habits
   a. Mouth breathing
   b. Tongue thrusting
   c. Thumb/finger sucking
   d. Grinding teeth
   e. Biting lips/tongue/cheeks/fingernails
8. Dietary habits (sugar intake)
9. Tobacco habits (frequency × years) or quit
   a. Pack Year: The risk of development of diseases due to tobacco smoking is related to the intensity of the exposure, frequently expressed in terms of "pack year." Pack year is a way to measure the amount a person has smoked over a long period of time. It is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. For example, 1 pack year is equal to smoking 1 pack per day for 1 year, or 2 packs per day for half a year, and so on.
10. Alcohol habits (frequency × years), (type of alcoholic beverage) or quit

Specific alcoholic beverages have been shown to contain specific impurities or contaminants which can be carcinogenic. N-nitrosodiethylamine is present in some beers and whisky and has been associated with an increased risk of oral cancer. Polycyclic aromatic hydrocarbons, some of which are considered to be carcinogenic are found in many brands of whisky. However, Kabat and Wynder (1989) concluded that the "main carcinogenic agent in alcoholic beverages is ethanol *per se* (in and of itself)." It must be also borne in mind that polycyclic aromatic hydrocarbons and nitrosamines are also widely present in tobacco and foodstuffs.

Medical History

A general medical history should be taken at the initial appointment to assist in proper diagnosis and treatment, and to allow safe dental care. This can be accomplished using a suitable questionnaire and accompanying verbal discussion. In situations where the patient has trouble reading, the dentist may take the medical history orally and make appropriate notes on behalf of the patient. It may also be necessary to obtain medical information from family members if the patient is unable to provide it (e.g., language barrier, Alzheimer's patient).

Any drug allergies, current drug regimens, medical alerts or conditions appropriate to the patient should be prominently noted on the patient record. This history should be updated at regular intervals and this fact noted in the patient record. It is important that the collection of necessary medical history information be done in a systematic manner. In doing so, the following key areas must be addressed for all patients and both positive and negative responses recorded:

1. Family history of disease
2. Adverse reactions to any medicines or materials e.g., penicillin, aspirin, erythromycin, local anesthetics, latex allergy (latex gloves and latex rubber dams)
3. Drug or alcohol dependency
4. A listing of all medications currently being taken
5. Details of past hospitalizations
6. List of surgical procedures
7. Women (pregnancy, birth control pills)
8. Cardiovascular disorders e.g., angina pectoris, myocardial infarction, congestive cardiac disease, hypertension, valvular disease, rheumatic fever, stroke etc

9. Respiratory disorders e.g., bronchitis, asthma, tuberculosis, emphysema, cystic fibrosis etc
10. Neurological disorders e.g., epilepsy, Bell's palsy, cerebral palsy, Alzheimer's disease, etc
11. Hematological disorders e.g., anemias, leukemias, lymphomas, bleeding disorders
12. Endocrine disorders e.g., hyperthyroidism, hypothyroidism, hyperparathyroidism, diabetes mellitus etc
13. Gastrointestinal disorders e.g., gastritis, peptic ulcer, jaundice, cirrhosis, hepatitis etc
14. Renal disorders e.g., acute and chronic renal failure etc
15. Dermatological disorders e.g., eczema, fungal infection, psoriasis etc
16. Psychiatric disorders e.g., anxiety, depression, schizophrenia, bipolar disorder etc
17. Nutritional disorders e.g., anorexia nervosa, bulimia etc
18. Infectious diseases e.g., AIDS, syphilis, infectious mononucleosis etc
19. Cancer/radiation treatment /chemotherapy
20. Organ transplants (solid organs or bone marrow)
21. Medical implants (joint replacement, heart valve replacement, pacemaker, indwelling catheters)
22. Ever had or been tested positive for any immunocompromising disease

Clinical Examination

The clinical examination is tailored to the patients chief complaint. A visual examination should precede other diagnostic procedures. The clinical examination consists of recordings on an odontogram *(tooth chart)* which may include written descriptions of the conditions (e.g., decayed teeth, missing teeth, and restored teeth) that are present on examination of the patient. However, other conditions such as intrinsic staining and hypoplasia require separate written descriptions. It is important that there is sufficient space to record all relevant information and to update it whenever necessary. For those patients with little or no history of dental disease and relatively healthy oral tissues, this can be accomplished with a notation such as "nothing abnormal detected" for most of the areas. Components of a comprehensive clinical examination include:

1. Examination of patients chief complaint
2. Vital signs (temperature, respiratory rate, pulse, blood pressure)
3. Pallor, icterus, cyanosis, and clubbing
4. Extraoral
   a. General appearance (well build, moderately build, ill build)
   b. Height, weight, and gait
   c. Facial symmetry (symmetrical, asymmetrical)
   d. Facial profile (convex, straight, concave)
   e. Head (normal, brachycephalic *(short head)*, dolichocephalic *(long head)*)
   f. Eyes (normal, exophthalmia, enophthalmia, hypertelorism *(increased intercanthal distance)*, strabismus or squint *(convergent or divergent)*, blue sclera)
   g. Nose (normal, saddle nose, parrot's beak)
   h. Neck
      I. Lymph nodes (Figs 1.1A to E)
         i. Size: Estimate the size in millimeters
         ii. Number: Single or multiple enlarged lymph nodes
         iii. Location: Unilateral or bilateral
         iv. Tenderness: When palpated the lymph node may be painful (tender) or not painful (nontender)
         v. Mobility: When palpated the lymph node may be fixed to the underlying tissue or freely movable under the fingers
         vi. Consistency: Describe the lymph node as hard (stone), firm (like a tensed muscle), soft (like a water balloon)
      II. Other neck masses (thyroglossal duct cyst, epidermoid cyst, dermoid cyst,

Fig. 1.1A: Palpation of the submandibular lymph nodes

Fig. 1.1B: Palpation of the submental lymph nodes

Fig. 1.1C: Palpation of the upper jugular lymph nodes

Fig. 1.1D: Palpation of the middle jugular lymph nodes

Fig. 1.1E: Palpation of the lower jugular lymph nodes

submental lymphadenitis, submental abscess, thyroid gland tumors, ectopic thyroid, carotid body tumor, branchial cleft cyst, cystic hygroma, neurofibroma, fibroma, hemangioma, plunging ranula, salivary gland tumors, sialoadenitis, esophageal fibroma, sarcoidosis, metastatic carcinoma, intrathoracic goiter)

i. Muscles of mastication (normal, hypertrophied, paralyzed)
j. Salivary glands (normal, enlarged)

5. Temporomandibular joint examination
   a. Assessment of pain location
   b. Opening pattern
   c. Vertical range of movement (Fig. 1.2A and B).
   d. Joint sounds on vertical opening
   e. Jaw excursions (lateral and protrusive)
   f. Joint sounds on lateral and protrusive excursions

Fig. 1.2A: Unassisted mandibular opening without pain

Fig. 1.3A: Palpation of the lateral pole

Fig. 1.2B: Maximum assisted mandibular opening

Fig. 1.3B: Palpation of the posterior disc attachment

g. Muscle and joint palpation
   i. Extraoral muscles
   ii. Temporomandibular joint (Figs 1.3A and B)
   iii. Intraoral muscles (Figs 1.4A and B)

6. Intraoral soft tissue examination
   a. Lips
   b. Labial mucosa
   c. Buccal mucosa
   d. Buccal vestibule
   e. Retromolar area
   f. Oropharynx
   g. Palate (hard and soft)
   h. Lingual vestibule
   i. Tongue (posterior, dorsal, lateral, ventral)
   j. Floor of mouth
   k. Salivary gland ducts

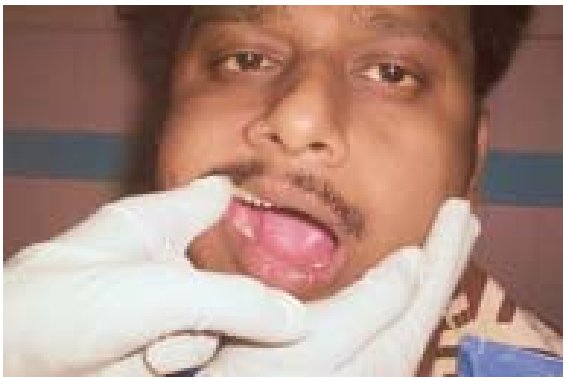

Fig. 1.4A: Palpation of the lataral pterygoid area

7. Intraoral hard tissue examination
   a. Appliances present
   b. Occlusion (Class I, Class II *(Div I, Div II)*, Class III)
   c. Overjet

Fig. 1.4B: Palpation of the tendon of temporalis

d. Overbite
e. Crossbite
f. Crowding
g. Spacing
h. Decayed teeth
i. Missing teeth
j. Restored teeth
k. Sensitive teeth
l. Impacted teeth
m. Supraerupted teeth
n. Migrated teeth
o. Fractured teeth
p. Mobile teeth
q. Regressive alterations
r. Developmental disturbances
s. Edentulous (unerupted teeth, bony spicules, retained roots, shallow vestibule, hyperplastic tissue)

8. Periodontal examination
   a. Deposits (plaque, stains, calculus)
   b. Gingiva (size, shape, color, consistency, texture)
   c. Gingival bleeding or suppuration
   d. Gingival recession
   e. Frenal attachments (normal, high, low)
   f. Furcation involvement
   g. Probing of pocket depths when indicated

Diagnosis

Diagnosis is an assessment of the clinical findings, which may help in identifying a specific disease. There are a number of related terms, which are as follows:

1. Spot diagnosis
2. Working diagnosis (provisional diagnosis or tentative diagnosis)
3. Differential diagnosis
4. Definitive (final diagnosis)

Spot Diagnosis

Diagnosis made quickly on the spot. It can be a perfectly good diagnosis e.g., a patient returns three days after removal of a tooth complaining of pain, bad taste, exhibiting inflammation and discharge at the extraction site. The spot diagnosis is that the patient probably has a "dry socket." In such case, various diagnostic tests are not required unless the condition does not respond to the routine treatment.

Working Diagnosis (Provisional diagnosis or tentative diagnosis)

Diagnosis made when the clinical presentation corresponds to a particular disease so that preliminary treatment may proceed. Example, ulceration on the lateral border of the tongue in relation to a sharp edge of a grossly decayed tooth may simply be a traumatic ulcer in response to chronic irritation. With that as a working diagnosis, the sharp edge of the tooth may be grinded off or the tooth extracted and a reevaluation of the patient scheduled after a week or two. If the ulcer resolves, the clinician can safely and finally diagnose it as a "traumatic ulcer." However, if the ulcer has not resolved, the working diagnosis is discarded, and further investigations started.

Differential Diagnosis

It is a process of identifying a specific disease from other diseases that may produce similar signs and symptoms. Once the diagnostician has listed all the diseases that produce similar signs and symptoms, an algorithm (a precise rule or set of rules specifying how to solve some problem) may be used or prepared, which may help in narrowing down the list of diseases. Further investigations may then be carried out, until a single disease or cluster of diseases remain. At that point, all additional investigations to confirm the diagnosis within the cluster of diseases are performed, leading to a definitive diagnosis.

Definitive (Final diagnosis)

Diagnosis derived after using differential diagnosis is the definitive or final diagnosis. Once the definitive diagnosis is derived, the suitable treatment is delivered. However, if the disease fails to respond to the treatment, it may be necessary to turn back to the differential diagnosis and try all over again.

In cases of soft tissue and bony diseases, histological examination of biopsy specimen often determines the final diagnosis. Hematological diseases or autoimmune diseases may be proved by hematological examination and serology. However, not all diseases can be diagnosed easily, as the range of abnormal is as wide as that of normal.

Investigations

Based upon the clinical examination, the dentist may employ additional diagnostic tools to complete the oral health assessment. Such diagnostic aids may include: percussion test, vitality tests, radiographs, photographs, vital staining, biopsy, fremitus test, butterfly test, transillumination test, caries activity tests, laboratory tests, and study casts.

Treatment Plan

The treatment plan would include specific information regarding the nature of the procedures, materials to be used, number of appointments needed to accomplish this care, behavior management techniques and fee for proposed procedures. The treatment plan should be supported by a complete and accurate clinical record and take into account the relative urgency and severity of the patients condition. The patients choice of treatment should be recorded along with the estimated costs.

Referrals and Consultations

Notes of referrals to specialists or other health care professionals as well as copies of correspondence and reports should be incorporated into the record. If a patient requests access to their dental records or reports from other practitioners, they must be disclosed. When a patient refuses to be referred to another specialist, a note should be made in the record and if possible, the note should be signed by the patient or legally authorized representative.

Follow-up Notes

An entry must be made in the patients record that accurately and objectively summarizes each visit. The following information should be included:

1. Date of visit
2. Reason for visit
3. Changes in the medical history, if any
4. Clinical findings
5. Diagnostic procedures
6. Treatment rendered
7. Local anesthetic used including type and quantity
8. Medication given to the patient
9. Referrals to specialists or other health care professionals and the results of such referrals

Emergency Treatment Record

A dental emergency exists if the person needs immediate relief of pain, or control of infection or bleeding. The emergency treatment record should include:

1. Personal information
2. Thorough medical history and relevant dental history
3. Findings of the emergency
4. Record of services performed
5. Record of prescriptions
6. Record of referrals
7. Record of follow-ups

Laboratory Record

This is a record containing particulars of purchases of all dental prosthetic, restorative or orthodontic devices and should include the following information:

1. Name of laboratory
2. Address of laboratory
3. Nature of device
4. Materials used
5. Date of device prescribed
6. Device prescribed for whom

Drugs Record

Drugs must be prescribed, administered by a dentist in accordance with the Drugs and Cosmetics Act and Rules. The following information must be recorded on the patients record:

1. Date of prescription
2. Name of drug
3. Strength of drug
4. Quantity of drug
5. Form of drug
6. Directions for use
7. Condition being treated

If the prescription is given by phone from outside the office, the details should be recorded on a piece of paper and later transferred to the patient record.

Financial Record

Fees charged and payments received must be recorded including date of the transaction, method of payment, and source (e.g., patient, third party payer).

Confidentiality

Dental records are collections of sensitive patient information compiled to allow dental practitioners to provide dental treatment, ensure continuity of services, and maintain optimal standards of care. Every effort must be made to ensure that the information provided by the patient is protected against unauthorized use or disclosure. Dentists must educate their employees with regard to maintaining the confidentiality of patient information.

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Chapter 2

Biopsy

INTRODUCTION

French dermatologist Ernest Henry Besnier coined the word *"biopsy"* in 1879. In Greek, it means *Bios* meaning life and *opsis* meaning vision. As the diagnosis made clinically is purely provisional, biopsy is essential for final diagnosis. There is no harm in supplementing the provisional diagnosis with biopsy even when the clinician is sure that the lesion is benign. However, the provisional clinical diagnosis is very important in guiding the biopsy technique.

Definition

According to Richard W.Tiecke, biopsy may be defined as surgical or non-surgical removal of tissue from a living organism for microscopic analysis, chemical analysis, or bacterial analysis or a combination of all.

1. **Microscopic analysis:** Histopathological examination or cytological examination
2. **Chemical analysis:** Protein estimation of aspirated fluid
3. **Bacterial analysis:** Bacterial culture

Types of Biopsy

1. Excisional biopsy
2. Incisional biopsy
   a. Intraoral punch biopsy
   b. Modified Ellis drill biopsy
3. Brush biopsy
4. Laser biopsy
5. Fine needle aspiration biopsy

Excisional Biopsy

Excisional biopsy is the total removal of the pathological tissue along with margin of normal tissue. It is indicated when the size of the pathological tissue is less than 2 cm.

Incisional Biopsy or Wedge Biopsy

Incisional biopsy is the partial removal of the pathological tissue along with margin of normal tissue. It is indicated when the size of the pathological tissue is more than 2 cm.

Intraoral Punch Biopsy

An alternative technique to the traditional incisional biopsy is the punch biopsy. The punch biopsy instrument has a circular blade attached to a plastic handle. The diameter of circular blade can be adjusted from 2 to 10 mm. The biopsy specimen can be removed with a help of curved scissors or a scalpel. There are chances that the biopsy specimen being sucked in. If the resultant wound is large, it is usually sutured. A study carried out by Moule *et al* (1995) has shown that punch biopsies produce fewer artifacts. The site of the lesion may indicate punch biopsy or

incisional biopsy. Lesions on the gingiva and palate do not give enough access for punch biopsy.

Modified Ellis' Drill Biopsy

Drill biopsy is a type of incisional biopsy, which is indicated in central lesions. The biopsy is performed under local anesthesia or general anesthesia, following which the mucoperiosteal flap is reflected and a window is made in the cortex with the help of bur. However, sometimes the cortex may be thin or perforated and bur is not required for window preparation. Once the cortex is removed the underlying pathology is exposed, which can be curetted and placed in 10% formalin.

Brush Biopsy

Majority of oral cancer cases are diagnosed in advanced stages as the early stages of oral cancer are asymptomatic and appear innocuous and the classical clinical characteristics associated with advanced oral cancer like ulceration, induration, bleeding, and cervical lymphadenopathy are absent. Thus, detection of oral cancer in the early asymptomatic stages dramatically improves patients survival rate and minimizes extensive debilitating treatment procedures. Therefore, the US Collaborative Oral CDx study group undertook a study to evaluate the sensitivity of Oral CDx (Oral Scan Laboratories, Inc.). The Oral CDx is a diagnostic system that combines a painless oral brush biopsy (full transepithelial oral biopsy), which is taken in the dental office, with advanced computer analysis. The Oral CDx oral brush biopsy test was developed precisely to evaluate benign-appearing oral lesions and was evaluated in a prospective multicenter clinical trial that involved 35 United States academic dental sites and the findings were published in the JADA, Vol.30, October 1999. Sullivan-Schein dental subsidiary of Henry Schein, Inc, exclusively distributes the Oral CDx oral brush biopsy. In comparison to exfoliative cytology Oral CDx, brush biopsy has an upper hand because of two reasons:

1. The dysplastic or cancerous cells are located deep to the keratin layer
2. The procedure consists of microscopic screening a cytological smear consisting of 1000's of normal cells to identify abnormal cells because the exfoliating normal cells are in enormous numbers because of epithelial turnover

Brush biopsy is also being effectively used in the medical field as a diagnostic tool for bronchial, duodenal, pancreatic, biliary, and rectal cancers. For more information on Oral CDx brush biopsy one can email to oralcdx@oralscan.com.

The Oral CDx brush biopsy kit is free and includes:

1. Sterile brush
2. Precoded glass slide
3. Alcohol or polyethylene glycol fixative pouch
4. Test requisition form, which includes patients demographic data
5. Preaddressed container

Advantages

The advantages of Oral CDx brush biopsy are enlisted below (Table 2.1).

Table 2.1: Advantages of Oral CDx brush biopsy

• Local anesthesia is not required
• Reduced chair side time
• Simple procedure which is easy to master
• Quick results

Indications

The indications of Oral CDx brush biopsy are enlisted below (Table 2.2).

Table 2.2: Indications of Oral CDx brush biopsy	
• Precancerous lesions	• Herpes simplex virus infection
• Oral squamous cell carcinoma	• Human papilloma virus infection
• Candidiasis	• Pernicious anemia
• Pemphigus vulgaris	• Radiation effects

Procedure

No local anesthetic is required. Slightly moisten the biopsy brush with the patients saliva if the lesion is dry. Press the biopsy brush firmly against the lesion. Rotate 5-10 times (depending on the thickness of the lesion) while maintaining firm pressure until pink tissue or pinpoint bleeding is observed. The cellular material collected on the brush is transferred to the precoded bar glass slide by rotating and dragging the brush lengthwise. The fixative packet is quickly squeezed onto the precoded bar glass slide to avoid air-drying. Set the slide aside to dry for 15 minutes, and then place it in the slide holder. Complete the test requisition form, and send the specimen to Oral Scan Laboratories in Suffern, N.Y. in the preaddressed container. At the Oral Scan laboratory, the precoded bar glass slide is stained with modified Papanicolau stain which is scanned by the Oral CDx computer for abnormal cells. The abnormal cells identified by the Oral CDx computer are displayed on the high-resolution colour video monitor for interpretation by a pathologist specially trained in computer-assisted analysis of oral brush biopsy specimen. The pathologist classifies the specimens displayed on the high-resolution colour video monitor into four categories, which are enlisted below (Table 2.3). After submitting the Oral CDx brush, biopsy specimen to the speciality laboratory the dentist receives a faxed report consisting of coloured images of the "atypical" or "positive cells." The coloured images enable the dentist to demonstrate to the patient the abnormal test results.

Oral CDx Computer

The Oral CDx is a nonalgorithimic neural network computer whose technology was developed in the late 1980s for SDI missile defense system. The Oral CDx computer is specifically designed to detect as few as two abnormal oral epithelial cells scattered among more thousands of normal cells distributed on each oral brush biopsy specimen. In addition, the Oral CDx computer also complements the existing oral cancer screening modalities that use vital dyes like toluidine blue. Toluidine blue is a metachromatic vital dye that increases visual detection of oral precancer and cancer after negative clinical examination. The nonalgorithimic neural network computer is a type of artificial intelligence that attempts to imitate the way a human brain works by creating connections between processing elements, the computer equivalent of neurons rather than a

Table 2.3: Classification of Oral CDx specimens		
Categories	**Interpretation**	**Action**
• Negative	No epithelial abnormality	Careful clinical follow-up
• Atypical	Abnormal epithelial changes of uncertain diagnostic significance	Refer for scalpel biopsy and histological evaluation
• Positive	Definite evidence of dysplasia or carcinoma	Refer for scalpel biopsy and histological evaluation
• Inadequate	Incomplete transepithelial biopsy	Repeat the brush biopsy procedure

digital computer, in which all computations manipulate zeros and ones. Neural networks are particularly effective for predicting events when the networks have a large database of prior examples to draw on. Bernard Widrow of Stanford University pioneered the field of neural networks in the 1950s. The nonalgorithimic neural network computer is currently used prominently in voice recognition systems, image recognition systems, industrial robotics, medical imaging, aerospace applications, and data mining.

Laser Biopsy

Lasers can be effectively used for incisional and excisional biopsies. Lasers have a definite edge over the conventional scalpel because of the following reasons:

1. Patient acceptance
2. There is little or no bleeding
3. Dry operating field
4. Excellent visibility
5. Reduced operating time
6. No trauma to adjacent tissues
7. Pain is reduced to 90 % due to sealing of nerve fibers
8. Bacterial counts are reduced thereby providing a relatively sterile operating field
9. There is little or no postoperative swelling due to sealing of blood vessels and lymphatics
10. Because of minimal bleeding and sealing of blood vessels and lymphatics chances of metastasis is eliminated when performing biopsy on oral squamous cell carcinoma

An important principle to remember is that even though the surgeon is employing laser as an alternative to scalpel the principles of the biopsy procedure are same for example the biopsy specimen should include both normal and pathological tissues. Focused mode is preferred over defocused mode because in focused mode, the intensity of the laser beam is high and the laser beam hits a focal spot on the tissue surface. For the patient and the surgeon eye protection is very essential, as the laser beams are harmful. Different lasers require different types of safety glasses and these should never be interchanged for example argon lasers require dark green safety glasses. General anesthetic gases should be kept away from laser beams as fires and explosions may be ignited when lasers hit them. In addition, instruments with reflective surfaces like mouth mirror, polished restorations should be kept away from lasers, as they tend to reflect the laser beam. The laser plume created when tissue vaporizes produces "fulguration artifact" in the biopsy specimen thus when laser biopsy is performed the pathologist should be informed. The surgical applications of dental lasers are enlisted below (Table 2.4).

Fine Needle Aspiration Biopsy

Aspiration biopsy is very inexpensive, quick and easily performed technique. The complete transtumor sample is composed of cells, tissue, or fluid and is useful in diagnosis of fluctuant lesions, deep-seated submucosal lesions and metastasis in enlarged cervical lymph nodes. A

Table 2.4: Surgical applications of dental lasers

• Fibroma	• Oral submucous fibrosis	• Mucous membrane pemphigoid
• Papilloma	• Oral squamous cell carcinoma	• Tongue lesions
• Epulis	• Aphthous ulcers	• Hemophilia
• Leukoplakia	• Herpetic lesions	• Idiopathic thrombocytopenia purpura
• Lichen planus	• Pemphigus vulgaris	• Slurge-Weber syndrome

10 ml syringe, 22-gauge needle, frosted glass slides, 10% formalin is all that is needed. The skin should be prepared with iodine prior to aspirating the enlarged cervical lymph nodes. The needle is inserted into the fluctuant swelling or the enlarged cervical lymph nodes and moved up and down. Once the cells, tissue, or fluid is aspirated, the needle is withdrawn from the swelling and sent for either protein estimation or cytological examination. The various colours of aspirated fluid are enlisted below (Table 2.5).

Table 2.5: Various colours of aspirated fluid

Pathology	Aspirate colour
• Odontogenic keratocyst	Thick yellow cheesy material
• Dentigerous cyst	Straw coloured fluid
• Radicular cyst	Straw coloured fluid
• Residual cyst	Amber coloured fluid
• Traumatic bone cyst	Nonproductive
• Aneurysmal bone cyst	Red coloured fluid
• Infected cyst	Pus
• Ameloblastoma	Straw coloured fluid
• Haemangioma	Red coloured fluid

Indications for Biopsy

1. Lesions that cannot be diagnosed by clinical and radiological examination
2. Lesions that which do not respond to treatment
3. Precancerous lesions and conditions
4. Lesions, which exhibit rapid growth, paresthesia, or loss of function
5. Cancerophobia

Contraindications for Biopsy

1. Acute inflammatory conditions such as cellulitis
2. Normal anatomical variations such as linea alba
3. Patients with bleeding disorders
4. Vascular lesions such as haemangioma
5. Patients who are on anticoagulant therapy

Principles of Biopsy Procedure

1. A written consent from the patient prior to the biopsy procedure is very important, as there are risks involved in biopsy procedures such as paresthesia, and swelling.
2. The type of biopsy will be based on the approximate size of the lesion. In case the size of the pathological tissue is less than 2 cm, excisional biopsy is preferred. Incisional biopsy is indicated when the size of the pathological tissue is greater than 2 cm.
3. During the biopsy procedure, consideration should be given to anatomical structures like neurovascular bundles that should be handled with care. For example when incisional biopsy of the palate is performed the incisions should run parallel to the nerves (antero-posteriorly) and not (medio-laterally).
4. In order to select the biopsy area vital stains like toluidine blue, lugol's iodine, or acridine help in identifying areas of dysplasia, carcinoma *in situ* and invasive carcinoma. Avoid biopsy from centre of large tumors, as they are necrotic.
5. Infiltration with a local anesthetic well away (atleast 2 cm) from the biopsy site is preferable as there are chances of biopsy specimen being distorted due to artificial water logging. Infiltration should be slow and minimal to prevent separation of epithelium from connective tissue and rapid swelling.
6. Nerve block is not preferred as the haemostatic effect of adrenaline is lost.
7. Insert 000 silk suture material into the pathological tissue and tie a loose knot above the tissue surface. The knot should not be very close to the tissue surface as the knot has a tendency to crush the lesion.

8. Elevate the 000 silk suture with the knot.
9. An elliptical-shaped incision is made around the pathological tissue with a scalpel, which should include normal adjacent tissue.
10. The size of the biopsy specimen should be atleast 1 × 1 cm in size, as inadequate size may pose problems such as shrinkage after fixation and there may be chances of repeat biopsy.
11. In case of excisional biopsy, the lesion should be oriented. This can be achieved by placing a suture at one known margin, for example the anterior or superior margin. This would enable the pathologist to confidently indicate the precise location of any residual tumor.
12. In order to avoid artifacts the biopsy specimens should be handled with care as improper handling may produce "crush defects." The 'traditional' technique using toothed tissue forceps to grasp the specimen is acceptable providing care is taken and the area grasped is away from the main site of interest.
13. The excised biopsy specimen is not placed in a bottle having narrow mouth and neck, as the biopsy specimen tends to get crushed. Rusted containers should be avoided, as iron oxide will interfere with staining.
14. The excised biopsy specimen is placed in 10 % neutral buffered formalin fixative, which has a pungent and distinct odour. The volume of the fixative should be atleast 10 times the volume of the specimen. It is not advisable to place the biopsy specimen on gauze and then place it in the glass bottle containing formalin because the gauze tends to absorb the formalin if its volume is not great enough. Glutaraldehyde is the fixative of choice if the biopsy specimen is required for electron microscopy. In case 10 % formalin is not available, the biopsy specimen should be placed in absolute alcohol. Normal saline or anesthetic solution may be used alternatively to prevent autolysis. "Michel's solution" is the choice of fixative in Vesiculo-bullous lesions and not 10% formalin as formalin fixes the biopsy specimens by forming intermolecular bridges between proteins and cross-links between protein end groups thus the specimen is rendered unusable for immunofluorescence test. Alternatively, the biopsy specimen can be immediately frozen.
15. Biopsy specimens from different anatomical sites should be placed in different containers and properly labeled.
16. Suture the surgical area with 000 silk non-resorbable suture material. Resorbable sutures such as polyglactin are now replacing traditional 000 silk sutures.
17. A non-eugenol containing periodontal dressing can be used for covering gingival biopsy sites and in case of palatal biopsies; a preconstructed acrylic plate should be placed beneath the non-eugenol containing periodontal dressing.
18. Securely seal the bottle and label it.
19. Fill up the biopsy form with the necessary details.
20. Send the biopsy specimen to the pathologist for microscopic examination.

Modifications of Biopsy Procedure (Table 2.6)

1. In diagnosis of precancerous lesions such as leukoplakia or erythroplakia, importance should be given to areas, which are non-homogenous, speckled, or erythematous as they have a higher incidence of having dysplastic features or transforming into malignancy. If there are numerous erythematous areas, multiple biopsies should be performed.
2. In diagnosis of lichen planus or lichenoid reactions, area of non-erosive lesional tissue should be chosen without adjacent normal tissue as erosive areas usually show non-

specific inflammatory changes and ulceration.

3. In diagnosis of oral cancer, a pie-shaped deep incisional biopsy specimen involving the margin of the ulcer along with 1 cm margin of normal mucosa, however, 2 cm margin of normal mucosa is indicated in squamous cell carcinoma of tongue. If the margin of normal mucosa is less than 1 cm, there is an increased recurrence rate of oral squamous cell carcinoma. The incisional biopsy should be deep involving submucosa to rule out extensive spread. A study carried out by Kinsukawa *et al* (2000) demonstrates that cytokeratins are present in the peripheral blood in two out of ten patients 15 minutes after incisional biopsy of an oral squamous cell carcinoma, thereby demonstrating that there was dissemination of cancer cells, which may result in metastasis.
4. Mucoceles should be excised completely with lot of care along with associated minor salivary glands as they have a tendency to recur.
5. In diagnosis of minor salivary gland tumors of the palate, incisional biopsy should be performed and should be as deep as possible because the lesions can be deep to the palatal mucosa. Due attention should be given to nerve and vessels of that area.
6. In diagnosis of vesiculobullous lesions such as pemphigus, the site of the biopsy should be adjacent to vesicle or bulla where the epithelium is normal.

Artifacts in Oral Biopsies

In order to investigate the various artifacts in oral biopsies, Seoane *et al* (2004) randomly selected 354 oral biopsy samples. The various artifacts

Table 2.6: Types of biopsies

Pathology	Type of biopsy
• Ameloblastoma	Incisional biopsy
• Cyst	Aspiration biopsy
• Epulis	Excisional biopsy
• Extraoral soft tissue swellings (Major salivary gland tumor)	Fine needle aspiration cytology (FNAC) Fine needle cutting biopsy (FNCB(
• Fibroma	Excisional biopsy
• Leukoplakia	Excisional biopsy Incisional biopsy Multiple incisional biopsies if lesion is extensive Punch biopsy
• Lichen planus	INcisional biopsy of non-erosive lesional tissue
• Minor salivary gland tumor	Deep incisional biopsy Punch biopsy
• Mucocele	Excisional biopsy
• Oral submucous fibrosis	Incisional biopsy
• Squamous cell carcinoma	Incisional biopsy involving the margin of ulcer
• Traumatic ulcer	Incisional biopsy involving the margin of ulcer
• Vesiculobullous lesions	Incisional biopsies of mucosa close to bufla, erosion, or ulcer Punch biopsy

identified by them were crush 27.1%; haemorrhage 19.8%; splits 11.3%; and fragmentation 6.2%.

Information to Accompany the Biopsy Specimen

1. Name of the doctor who has referred the biopsy
2. Type of biopsy
3. Fixative used
4. Patients demographic data
5. Description of lesion
6. Summary of clinical findings
7. Medical history if relevant
8. Provisional diagnosis
9. Radiographs
10. If the biopsy specimen contains calcified structures, the pathologist should be informed about it so that they are decalcified prior to processing and sectioning of the biopsy specimen because they may damage the microtome or specimen during sectioning.

Precautions to be Taken while Sending the Biopsy Specimen by Postal Service

1. The bottle containing the biopsy specimen should be tightly sealed
2. Sufficient absorbent material like gauze or paper napkins should be placed around the bottle in case there is an accidental spillage of the fixative
3. The bottle should be placed in a sealed plastic container, which is then placed in a cardboard box and secured properly
4. The cardboard box should be labeled "*Pathological Specimen – Handle with Care*"
5. Name and address of the sender should be clearly displayed

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Chapter

3

Orofacial Pain

DEFINITION OF PAIN

The International Association for the Study of Pain or IASP defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."

The Trigeminal Nerve

The gasserian ganglion consists of cell bodies, which have peripheral and central processes. The peripheral processes make up the afferents and are in the V_1, V_2, and V_3 divisions of trigeminal nerve (Fig. 3.1). The central processes make up the sensory root, which enters the pons.

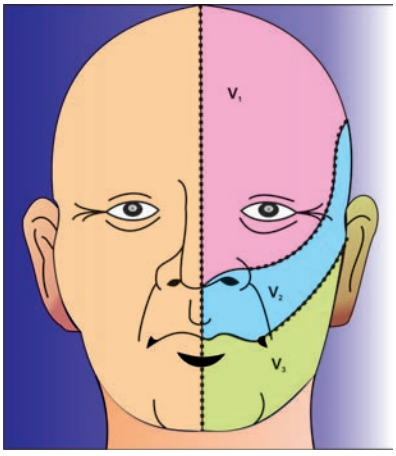

Fig. 3.1: Trigeminal nerve distributions

Components of Trigeminal Nerve

The trigeminal nerve has two components including:

1. Sensory component
2. Branchial motor component

Each trigeminal nerve division has proprioceptive fibres, touch, and pain, and temperature fibres.

1. The large A–α fibers transmit proprioceptive information
2. The A–β fibers transmit touch information
3. The A–δ and C fibers transmit touch, itch, warmth, cold, and nociceptive information

Trigeminal Nucleus

The trigeminal nucleus consists of four parts (Fig. 3.2)

1. Mesencephalic nucleus
2. Principal sensory nucleus
3. Spinal nucleus
   a. Subnucleus oralis
   b. Subnucleus interpolaris
   c. Subnucleus caudalis
   d. Motor nucleus

Trigeminal Nerve—Sensory Component

The peripheral processes of A–β fibers transmit touch information. The central processes of these fibers arise from the gasserian ganglion and

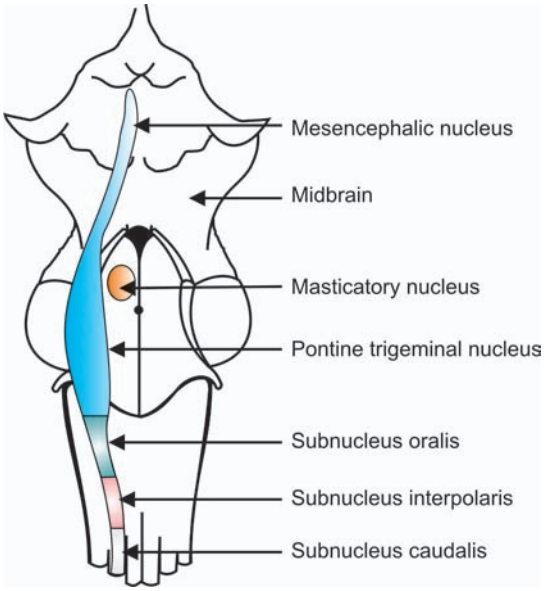

Fig. 3.2: Trigeminal nucleus

synapse in the principal sensory nucleus, subnucleus oralis, and subnucleus interpolaris. The principal sensory nucleus, subnucleus oralis, subnucleus interpolaris give rise to second order neurons which cross the midline (Fig. 3.3). The peripheral processes of A–δ and C fibers transmit touch, itch, warmth, cold, and nociceptive information. The central processes of A–δ and C fibers arise from gasserian ganglion and synapse in the subnucleus caudalis. The subnucleus caudalis give rise to the second order neurons, which cross the midline and ascend to join the second order neurons from principal sensory nucleus, subnucleus oralis, and subnucleus interpolaris as ventral trigeminothalamic tract (Fig. 3.4).

Trigeminal Leminiscus

The principal sensory nucleus gives rise to second order neurons, which ascend, ipsilaterally as dorsal trigeminothalamic tract. Both the dorsal and ventral trigeminothalamic tracts end in the ventro-posterior medial thalamic nuclei and comprise the trigeminal leminiscus (Fig. 3.5).

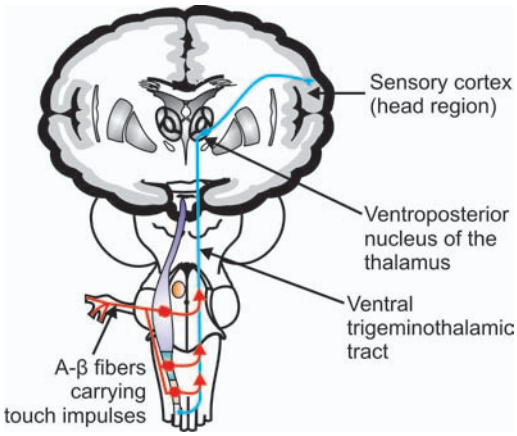

Fig. 3.3: Touch pathway

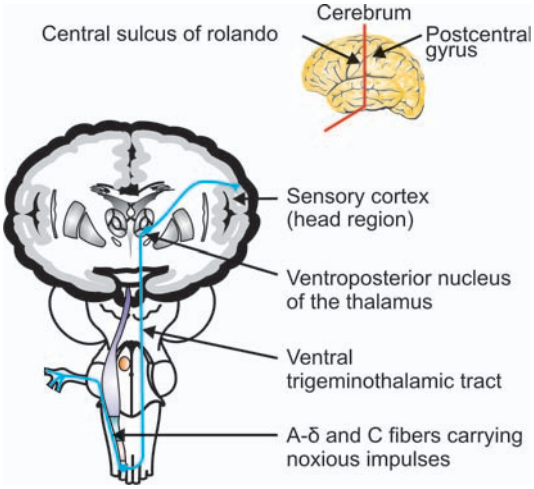

Fig. 3.4: Trigeminal nerve pain pathway

The Postcentral Gyrus

The third order neurons arise from the ventro-posterior thalamic nuclei and end in areas S1 (postcentral gyrus) and S2. The postcentral gyrus represents structures like mouth, teeth and has unilateral sensation (Fig. 3.6). The S2 area is present in the lower end of postcentral gyrus and has bilateral representation of the sensation.

TRIGEMINAL NEURALGIA

(Fothergill's disease, neuralgia epileptiformae, tic-doloureaux, trifacial neuralgia)

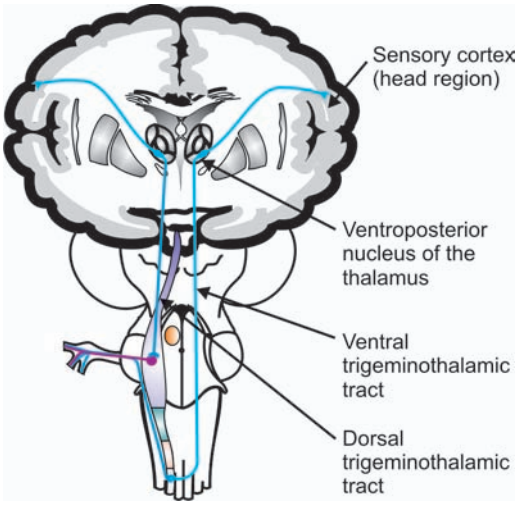

Fig. 3.5: Trigeminal leminiscus

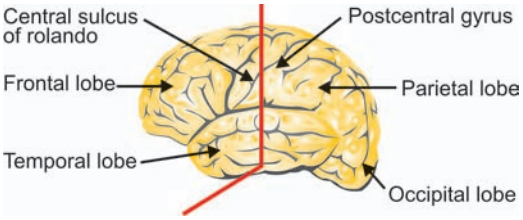

Fig. 3.6: Cerebrum

It is the most common facial neuralgia. Right side of face is frequently affected than left side. Pain is initiated by physical stimulation of specific areas known as trigger points or zones. Trigger zones (Fig. 3.7) are found in region innervated by trigeminal nerve. The physical stimuli may be touch, shaving, or brushing the teeth.

Classification of Trigeminal Neuralgia

1. Typical trigeminal neuralgia
2. Atypical trigeminal neuralgia
3. Pretrigeminal neuralgia
4. Multiple sclerosis related trigeminal neuralgia
5. Secondary or tumor related trigeminal neuralgia

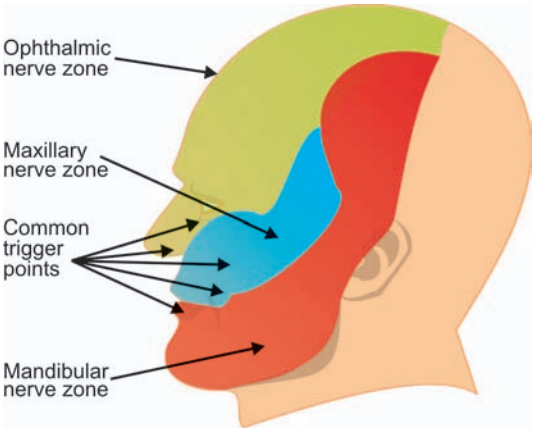

Fig. 3.7: Trigger zones

6. Posttraumatic trigeminal neuralgia
7. Failed trigeminal neuralgia

Etiology

1. Microvascular compression of the trigeminal nerve root
2. Failure of central inhibitory mechanism
3. Vascular disease of trigeminovascular system
4. Multiple sclerosis

Microvascular Compression of the Trigeminal Nerve Root

Microvascular compression of the trigeminal nerve root is most often caused by superior cerebellar artery which leads to the irritation of nerve root causing demyelination and ectopic firing resulting in hyperactivity in the trigeminal nucleus (Figs 3.8A and 3.8B). Hyperactivity of the trigeminal nucleus can lead to sudden painful attacks that last for seconds to 2 minutes. The painful attacks are accompained by tic-like cramps of the facial muscles and hence the name tic doloureux. Sixty percent of the cases involve V_2 and V_3. Trigeminal neuralgia is characterized

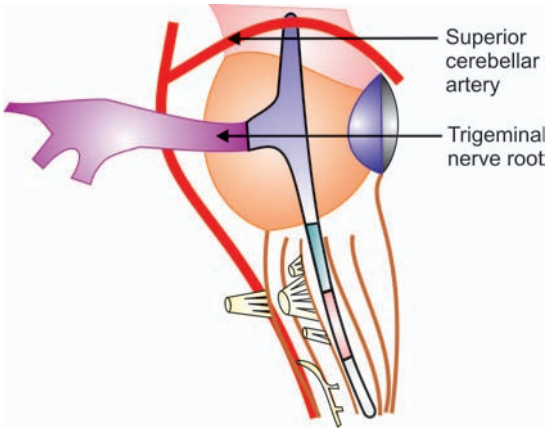

Fig. 3.8A: No vascular compression

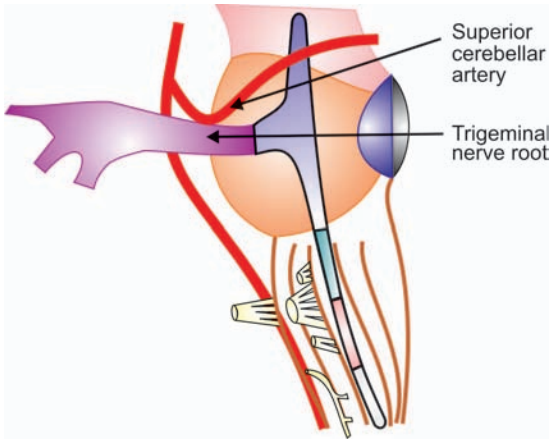

Fig. 3.8B: Vascular compression

by periods of exacerbation and remission. The periods of exacerbation are short early in the disease course and increases later (Fig. 3.9).

Treatment

1. Medical
2. Peripheral trigeminal nerve blocks
3. Surgical *(when medications fail)*
4. Radio surgery

Medical Treatment

The drugs used to treat trigeminal neuralgia reduce the hyperactivity of trigeminal nucleus.

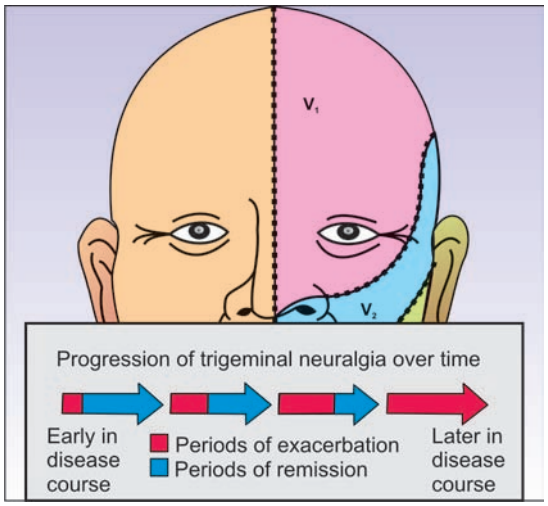

Fig. 3.9: Progression of trigeminal neuralgia

The various drugs used to treat trigeminal neuralgia include:

1. Carbamazepine—Antiepileptic drug (first drug of choice)
2. Phenytoin sodium—Antiepileptic drug (second drug of choice)
3. Baclofen—Muscle relaxant (second drug of choice)
4. Neurontin—Antiepileptic drug

Combination therapy is helpful when a single drug is not effective. Because of side effects and incomplete cure, most patients prefer to undergo surgical treatment. Figure 3.10 shows the medical treatment drug regimen given by Green *et al* (1991) and Figure 3.11 for adverse effects of medications.

Peripheral Nerve Block, Sectioning, and Avulsion

This procedure involves administration of peripheral nerve blocks, injection of alcohol, cutting (sectioning) of peripheral nerve and avulsion of the nerve. This procedure provides temporary relief and numbness and is indicated in patients who are unfit for surgery. As the recurrence rate is very high, surgery is the main treatment for long-term disease control.

Medication	Starting daily dose	Final daily dose
Carbamazepine	2 x 100 mg	400 - 800 mg
Baclofen	2 - 3 x 5 mg	60 mg
Phenytoin	2 x 100 mg	300 - 500 mg

Fig. 3.10: Drug regimen (Green et al, 1991)

Medications	Adverse effects	Others
Carbamazepine	Confusion, drowsiness, dizziness, diplopia, nausea, and vertigo	Agranulocytosis, leucopenia, and water retention
Baclofen	Ataxia, confusion, drowsiness, dizziness, fatigue, nausea, and weakness	Withdrawal effects like hallucinations, and tachycardia
Phenytoin	Ataxia, confusion, drowsiness, nausea, nystagmus, slurred speech, and vertigo	Gingival hyperplasia, and hirusitism

Fig. 3.11: Adverse effects of medications

Surgical Treatment

Surgical treatment includes:

1. Microvascular decompression surgery
2. Rhizotomies
   a. Microsurgical rhizotomy
   b. Percutaneous glycerol rhizotomy
   c. Balloon compression rhizotomy
   d. Percutaneous radiofrequency rhizotomy

Microvascular Decompression Surgery

The main aim of microvascular decompression surgery is to alleviate microvascular compression from the trigeminal nerve root. It is preferred open surgical method to treat trigeminal neuralgia.

Procedure

1. Hair is shaved and a small incision in made behind the ear under general anesthesia, following which a opening is made to gain access. This procedure is termed as suboccipital craniotomy (Fig. 3.12)
2. With the help of operating microscope, the surgeon looks for the area of microvascular compression caused by superior cerebellar artery
3. Shredded Teflon® felt implants are used in microvascular decompression surgery because they are inert and do not react with the local environment
4. Microinstruments are used to mobilize the offending vessels and to place the inert shredded Teflon® felt implants (Fig. 3.13)
5. Closing of the bony opening and suturing the skin, marks the end of the surgery (Fig. 3.14)

Complications

1. Hearing loss
2. Facial anesthesia

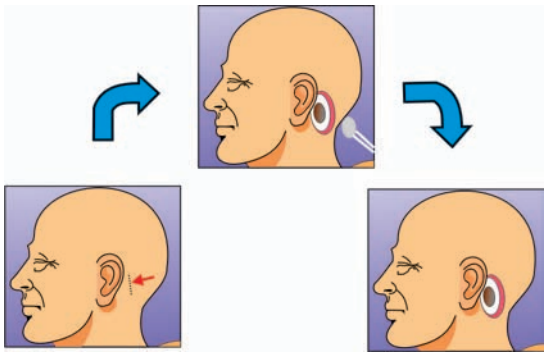

Fig. 3.12: Incision and craniotomy

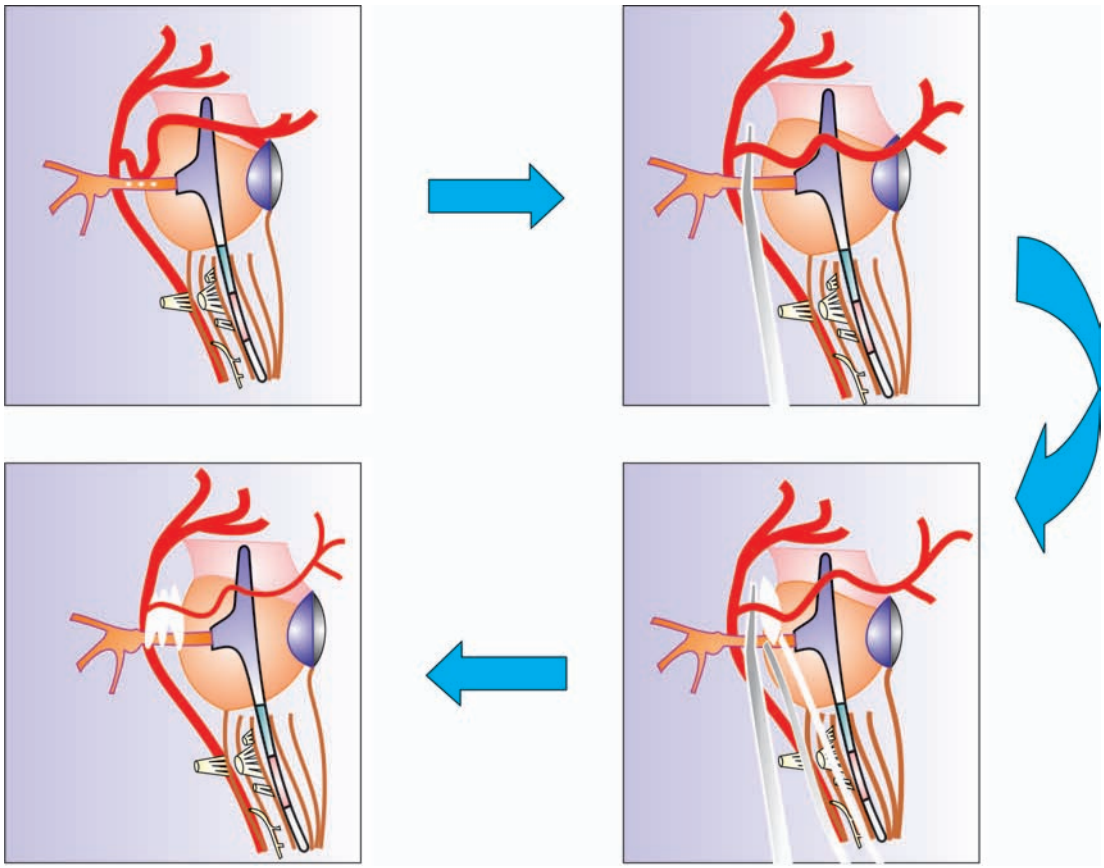

Fig. 3.13: Insertion of Teflon implants

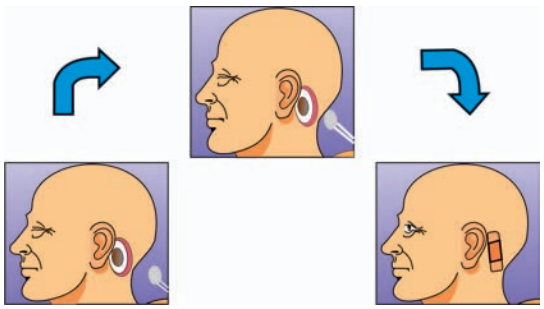

Fig. 3.14: Closing and suturing

3. Inflammation
4. Postoperative infection
5. Delayed healing
6. CSF leak
7. Cerebellar damage
8. Brain stem infarction
9. Stroke
10. Ataxia (muscular incoordination)
11. Death

Rhizotomies

Rhizotomy is destruction of ganglion and sensory root. Indicated when medications fail.

Types of Rhizotomies

1. Percutaneous glycerol rhizotomy
2. Balloon compression rhizotomy
3. Percutaneous radiofrequency rhizotomy
4. Microsurgical rhizotomy

Complications of Rhizotomies

1. Permanent facial numbness or anesthesia dolorosa
2. Temporary weakness in muscles of mastication
3. Loss of sensation of cornea, which can lead to keratitis and blindness

Percutaneous Glycerol Rhizotomy (Fig. 3.15)

Performed under local anesthesia. Needle is inserted through the foramen ovale to the gasserian ganglion. Radiograph is taken to guide the needle to the gasserian ganglion. The glycerol produces mild injury to the ganglion, which results in facial numbness. Usually, there is recurrence of pain.

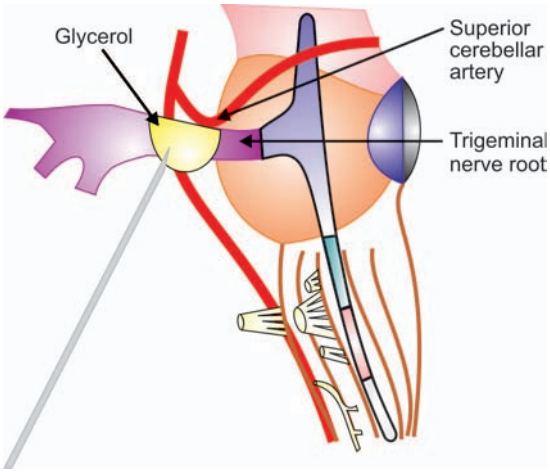

Fig. 3.15: Glycerol rhizotomy

Balloon Compression Rhizotomy (Fig. 3.16)

Performed under general anesthesia. Regarding pain control, this surgical procedure has greater potential than glycerol rhizotomy. The needle is 10.5 cm long, 14 gauge and is made up of stainless steel. Once the needle is placed near the gasserian ganglion, a 4.0 french silicone balloon catheter is introduced through the needle. The balloon is inflated causing injury by compression to the gasserian ganglion and nerve root. Effective when V_1 is involved

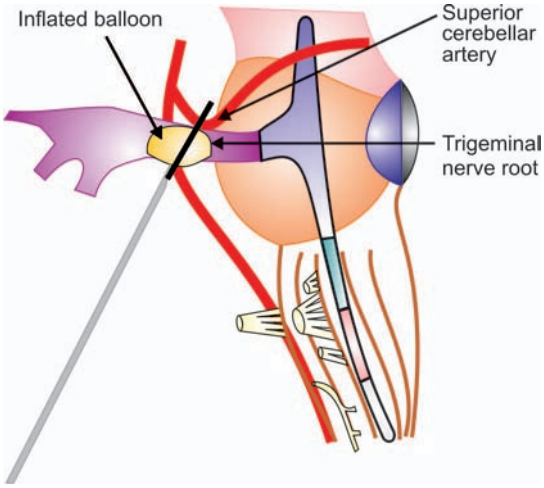

Fig. 3.16: Ballon compression rhizotomy.

Components in Mullan Set (Fig. 3.17)

1. Beveled access needle and sharp stylet
2. Blunt obturator
3. Scalpel
4. Syringe
5. Microcompression balloon catheter

Complications

1. Facial numbness
2. Weakness of muscles of mastication
3. Loss of sensation to cornea

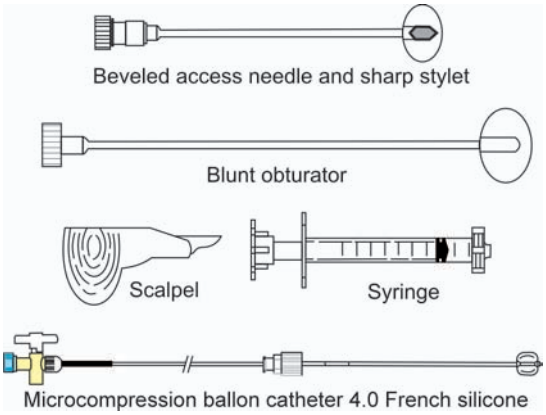

Fig. 3.17: Mullan compression set

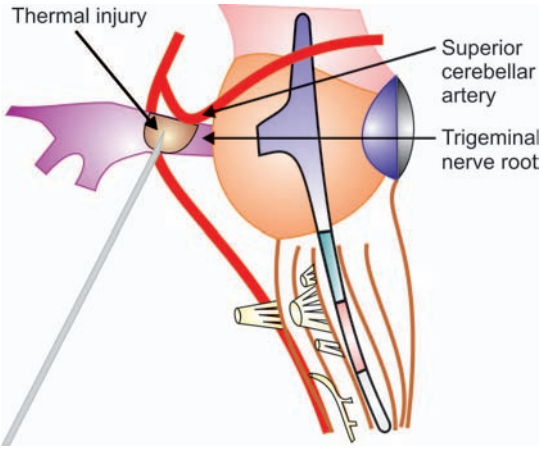

Fig. 3.18: Radiofrequency rhizotomy

Percutaneous Radiofrequency Rhizotomy (Fig. 3.18)

Performed under intravenous sedation. An electrode is placed at the gasserian ganglion. The electrode is heated with radiofrequency current causing thermal injury to the ganglion. Complications may include facial numbness.

Microsurgical Rhizotomy

Indicated when V_3 is involved. The trigeminal nerve root is sectioned. Complications may include numbness of the lower part of face. It has now been replaced by microvascular decompression surgery.

Gamma Knife Radiosurgery

In 1951 Lars Leksell, Professor of Neurosurgery in Sweden, introduced the concept of radiosurgery. The Gamma Knife® is a remarkable tool that allows surgeons to operate on abnormal areas of the brain and its surrounding tissue without making an incision (Fig. 3.19). Using a technique called stereotactic radiosurgery, it is designed to precisely target and destroy abnormalities within the head using highly focused gamma rays.

Patients experience minimal pain and in most cases, can resume their regular activities within a day or two after treatment. It is one of the most advanced techniques in the treatment of disorders affecting the brain and its adjacent structures. Gamma Knife treatment is not experimental. The Gamma Knife has been in use for over 30 years, and has been used successfully to treat more than 100,000 patients worldwide. Therefore, it is not surprising that the Gamma Knife is regarded as the "gold standard" for stereotactic radiosurgery.

Lesions Treated by Gamma Knife Radiosurgery

1. AV malformations
2. Meningioma
3. Gliomas
4. Acoustic neuromas
5. Pituitary tumors
6. Parkinson's disease
7. Metastatic tumors
8. Trigeminal neuralgia
9. Epilepsy
10. Glaucoma
11. Cluster headache
12. Uveal melanoma

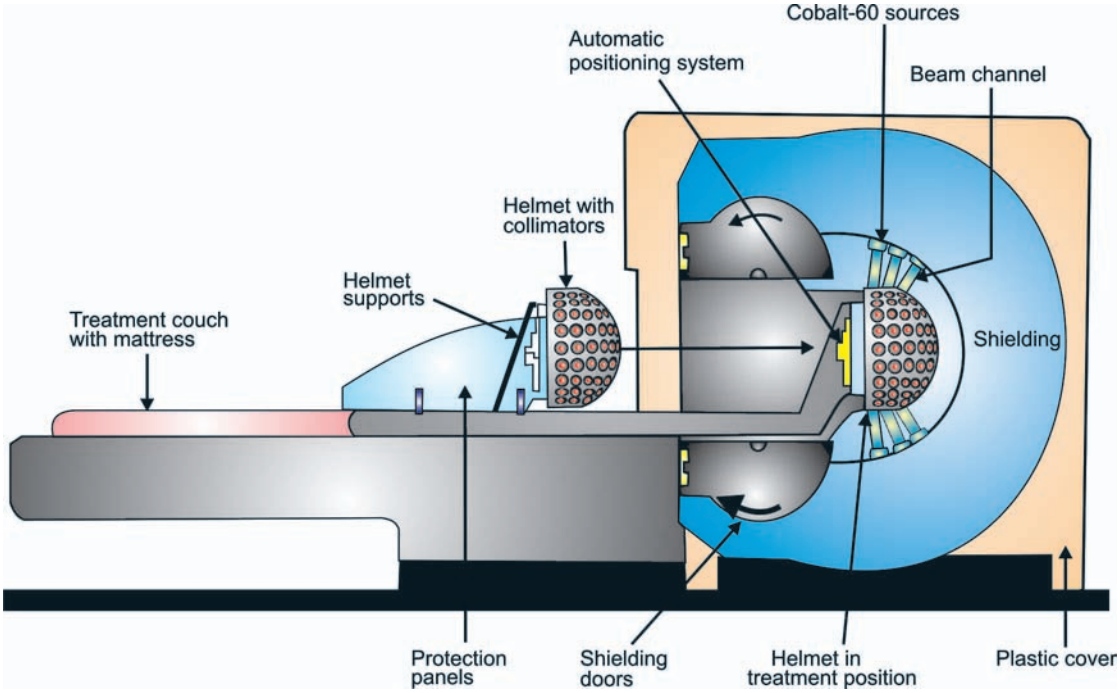

Fig. 3.19: Gamma knife unit

The Gamma Knife Team

1. Neurosurgeon
2. Radiation oncologist
3. Medical radiation physicist
4. Anesthesiologists (children)
5. Nursing staff

Treatment Procedure

The stereotactic frame is attached at four points around the patients head with pins that penetrate about 2 millimeters. To prevent any discomfort when the frame is attached, the patient is given local anesthesia (injected just under the skin). Frame fitting usually takes about 20 minutes. The function of the frame is to prevent the head from moving during imaging and treatment so that the radiation is delivered accurately and to establish spatial references. With the patient wearing stereotactic frame, MRI is taken to determine size and shape of lesion. The digital image is then transferred to Leksell Gamma Plan® computers installed with Leksell Gamma Plan® software, which allows the gamma knife team to:

1. Determine the exact relationship between the target lesion and the stereotactic frame.
2. Calculate how to set the controls of the gamma knife to treat the targets optimally with an accuracy of within 0.1 millimeter.
3. To calculate the dose and exposure time.

Once treatment planning is complete, the patient is moved to the treatment room that houses the gamma knife unit. The patient then lies down on the couch of the gamma knife, and the head is positioned in the appropriate collimator helmet (Fig. 3.20). The gamma knife unit contains 201 cobalt ^{60} sources of

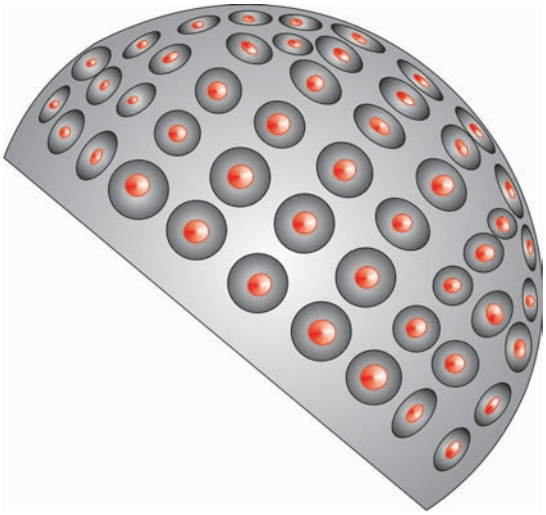

Fig. 3.20: Helmet

approximately 30 curies each, arrayed in a hemisphere. Cobalt ^{60}decays into Nickel ^{60} and one electron plus two gamma rays (Fig. 3.21). 201 focused beams of gamma rays are produced (Fig. 3.22). The gamma rays produced are aimed through a collimator to a common focal point with extreme accuracy of better than 0.33 mm. The trigeminal nerve root is the common focal point and receives a therapeutic dose of gamma rays. The surrounding brain tissue absorbs minimal gamma rays. Higher doses of gamma rays result in better pain control.

The diameter of collimators can be 4 mm, 8 mm, 14 mm, and 18 mm depending on size of gamma rays needed to accurately target the lesion. There are no loud noises during the treatment. A video and two-way voice communications system allows the patient to be in contact with the gamma knife team throughout the treatment. The patient may also listen to his/her own favorite compact disc. The total time the patient will be exposed to radiation usually ranges from 15 to 60 minutes but may be up to several hours, depending on the complexity of the treatment. The couch will automatically move out of the unit when the treatment is

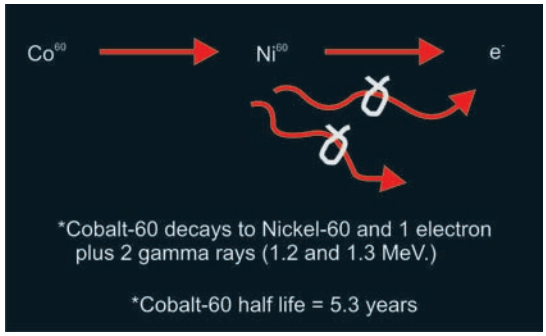

Fig. 3.21: Production of gamma rays

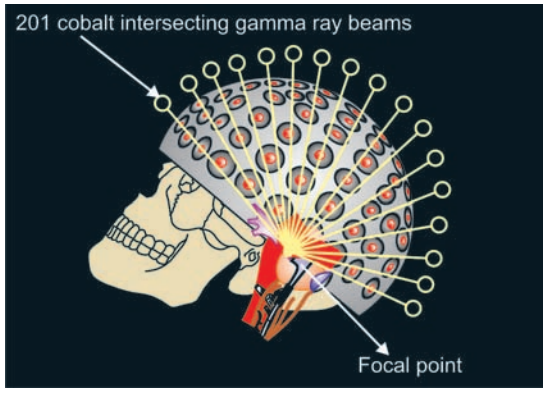

Fig. 3.22: Principles of gamma knife therapy

finished. After the treatment, the stereotactic frame is removed. There is no need for postanesthesia recovery or intensive care unless the treatment was carried out under general anesthesia especially children. The patient will probably be discharged from the hospital the following day. As the patients experience minimal pain, most people can resume their regular activities within a day or two after treatment.

Advantages

1. State-of-the-art technology
2. Supported by extensive study
3. Noninvasive
4. Precise and accurate

5. Safe
6. Good clinical outcome
7. Mortality rate is less
8. No convalescence (recover health after illness)
9. Cost-effective
10. The time factor

Complications

1. Headache
2. Scalp tenderness
3. Swelling
4. Cranial nerve dysfunction
5. Focal brain swelling
6. Focal brain necrosis

ATYPICAL FACIAL PAIN

Introduction

Unfortunately, there is a lack of a uniform definition and overall accepted diagnostic criteria of atypical facial pain or AFP. In the past, the term AFP served as a diagnostic "wastebasket" for facial pains that are not classified. Because of the vagueness of this term, the IASP discontinued to list AFP in their classifications of chronic pain. Instead, the broader term AFP has been replaced by two specific subentities, namely:

1. Atypical odontalgia (phantom tooth pain)
2. Glossodynia and sore mouth (oral dysesthesia)

However, in the clinical environment the term AFP is still widely accepted.

ETIOLOGY AND PATHOPHYSIOLOGY

The cause and pathophysiology of AFP remain enigmas. There are several theories about the pathophysiology of AFP. In general, the symptoms of AFP are initiated or reinforced by a local, often surgical trauma *(such as, extraction of teeth and interventions on the maxillary sinus)*. One view has AFP as a psychosomatic disease and is associated with anxiety and depression. An alternative theory states that AFP is a disease of trigeminovascular system. Other authors state that some aspects of AFP can be seen as a form of reflex sympathetic dystrophy *(regional pain syndrome)*.

Both AFP and regional pain syndrome share common features such as, the initiating noxious stimuli are of low intensity and there is pain relief after sympatholytic intervention.

Clinical Features

1. **Age:** Around 35-40 years
2. **Sex:** More commonly seen in women
3. **Anatomical location:** Usually one side of the face is affected, but bilateral occurrence is not uncommon

Clinical Presentation

AFP is characterized by an intense, deep, and constant pain. The pain is burning or aching, and it is poorly localized. AFP does not follow anatomical pathways of the peripheral nerves. Allodynia, dysesthesia, and paresthesia are common additional complaints. Unlike trigeminal neuralgia, eating, talking, and other facial functions are usually not impaired. Majority of the patients with AFP have no limitations in their ability to work. Sleep is not affected.

Treatment

AFP is considered the least manageable form of chronic pain. However, even small neurodestructive interventions carried out for therapeutic purposes generally aggravate the pain. Tricyclic antidepressants, such as amitriptyline, as well as MAO inhibitors (Selegiline Hcl) have been successful in specific cases. Another alternative is the use of benzodiazepines e.g., clonazepam. Additional treatment options include:

1. Transcutaneous electric nerve stimulation (TENS)
2. Psychotherapy
3. Sympathetic nerve blocks

BURNING MOUTH SYNDROME

(Stomatodynia, stomatopyrosis, oral dysesthesia) "Burning mouth syndrome" or BMS is a condition characterized by burning and painful sensations in a mouth with normal mucosa." When the symptoms of the burning mouth are limited to the tongue the term "glossodynia" is preferred.

Clinical Features

1. **Age:** 40-49 years (females) and 30-59 years (males)
2. **Sex:** Most frequent in women beyond middle age
3. **Sites:** Tongue, denture bearing mucosa, lips and buccal mucosa are the most frequently affected sites

Symptoms

Almost all patients with BMS describe their symptoms as "a burning feeling." Patients with BMS frequently describe other symptoms such as:

1. Xerostomia
2. Altered or loss of taste sensation

Assessment

To assess how severe is the burning sensation a linear analogue scale is used. On the scale the score "0" means no burning and "10" indicates intolerable burning. In a study by Lamey and Lamb 1988, they found a median score of "8."

Classification

Basker *et al* (1978) divided BMS into:

1. Mild
2. Moderate
3. Severe

They noted that moderate BMS is the most frequent, followed by the severe and mild forms. Furthermore, Basker *et al* (1978) reported that intermittent BMS was more common than continuous BMS.

Lamey and Lewis (1989) proposed three patterns of BMS as it might vary over the day (Fig. 3.23).

Type 1 is characterized by a symptom free period in the morning and burning sensation increasing during the day to be the most severe in the evening.

Type 2 is characterized by continuous burning sensation over the day.

Type 3 is characterized by symptom free periods over the day.

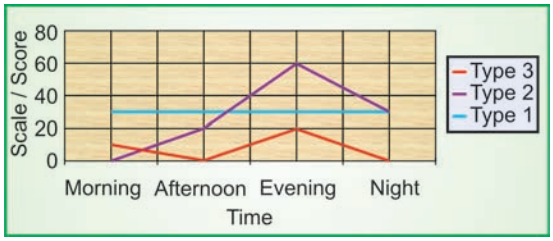

Fig. 3.23: Patterns of BMS

Etiological Factors

BMS is considered multifactorial and the etiological factors may be divided into three main groups:

Local Factors

1. Xerostomia
2. Candidiasis
3. Fusospirochetal infection
4. Local allergic reactions to Hg and denture based materials
5. Temporomandibular joint dysfunction

Systemic Factors

Systemic etiological factors, which might cause BMS, can be divided into the following main groups:

1. Deficiencies of different types
2. Hormonal disturbances
3. Immunological disturbances

Deficiencies

1. Fe deficiency
2. B_1, B_2, B_6, B_{12} deficiency
3. Combined deficiency of these vitamins
4. Folic acid deficiency

Hormonal and Immunological

Lamey and Lamb 1988, singled out diabetes mellitus as a possible etiological factor for BMS. As xerostomia was a frequent accompanying symptom in patients with a number of immunological disorders, Grushka *et al* (1987) emphasized the importance of immunological disorders as one of the etiological factor.

Psychogenic Factors

1. Anxiety
2. Depression
3. Neurosis
4. Psychasthenia
5. Cancerophobia
6. Dependent personality disorder

Treatment

BMS protocol to evaluate the BMS

1. Oral and medical investigations
2. Diagnosis of oral and medical diseases
3. Treatment of diagnosed oral and medical diseases
4. In patients with resistant BMS, a psychological examination is performed, followed by psychotherapy

BMS Protocol

The BMS protocol is a questionnaire, which is given to the patient to identify, the:

1. Location of the burning mouth symptoms
2. Description of the symptoms
3. Estimation of the intensity of the symptoms
4. When do these symptoms occur?
5. Time of the day these symptoms occur
6. Factors aggravating the symptoms
7. Factors relieving the symptoms
8. Any altered taste sensation
9. Any other symptom

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Chapter 4

Temporomandibular Joint Dysfunction

TEMPOROMANDIBULAR JOINT (TMJ) ANATOMY

INTRODUCTION

The temporomandibular joint is a unique joint as:

1. It functions bilaterally in unison
2. The articular disc is movable during the joint movements
3. The articular surfaces are covered by fibrocartilage and not hyaline cartilage
4. The fibrocartilage is considered as the growth center, which contributes to the overall growth of mandible (endochondral ossification)

TMJ SYNONYMS

1. Ginglymus joint
2. Diarthrodial joint
3. Mandibular joint
4. Synovial joint
5. Craniomandibular articulation

Classification of Joints (Fig. 4.1)

1. **Fibrous joints:** The two bones are connected by fibrous connective tissue
2. **Cartilaginous joints:** There are two types of cartilaginous joints, primary and secondary
   a. Primary: In a primary cartilaginous joint, the bone and cartilage are in direct collocation, e.g. costochondral junction.
   b. Secondary: In a secondary cartilaginous joint, the articulation tissues are in the sequence, bone-cartilage-fibrous tissue-cartilage-bone, e.g., pubic symphysis.
3. **Synovial joints:** The synovial joints consist of two bones, covered by hyaline cartilage, united and surrounded by a capsule

Type of joints	Examples
Fibrous Joint	Sutures Tooth Socket
Cartilaginous Joint	Costochondral Junction Pubic Symphysis
Synovial Joint	Temporomandibular Joint Knee Joint

Fig. 4.1: Classification of joints

Type of Joint

The TMJ (Fig. 4.2) is a synovial joint between the condylar head and articular fossa of the squamous part of temporal bone. It is a synovial

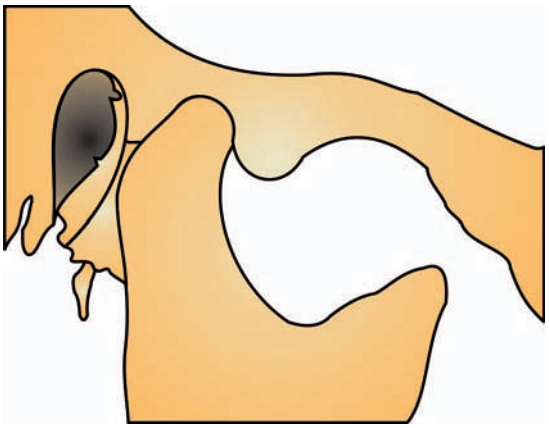

Fig. 4.2: Temporomandibular Joint

joint as the joint cavity is filled with synovial fluid. The TMJ differs from other synovial joints as its articular surfaces are covered by fibrocartilage and not hyaline cartilage. It is often said that the TMJ is not weight-bearing joint as its articular surfaces are covered by fibrocartilage and not hyaline cartilage. This statement is not true: the joint is weight bearing.

Structures Involved in the TMJ

1. Articular eminence
2. Articular fossa
3. Condyle
4. Capsule
5. Ligaments
6. Synovial lining
7. Articular disc

Articular Eminence

It is bony eminence present on the inferior aspect of the zygomatic process of the temporal bone. The lateral aspect of the articular eminence is often referred to as articular tubercle. However, it is important to note that the two terms articular eminence and articular tubercle are used synonymously by many authors.

Articular Fossa

It is a depression anterior to the external auditory meatus, which is limited anteriorly by articular eminence and posteriorly by posterior glenoid process or posterior glenoid tubercle. The center of the articular fossa is thin and it is possible to drive the condyle into the middle cranial fossa by a powerful blow to the mandible.

Fibrous connective tissue: A layer of avascular fibrous connective tissue forming the articular zone, lines the articular eminence, condylar head and, articular fossa. The avascular fibrous connective tissue consists of collagen fiber bundles with fibroblasts situated between the fiber bundles. The number of fibroblasts decreases with age. The avascular fibrous connective tissue is thickest on the articular eminence especially on the posterior slope. This is mainly an adaptation to the stress generated when the condyle and articular disc glide across the posterior slope of articular eminence. The thickness of avascular fibrous connective tissue on the condylar head is thick in comparison to articular fossa where it is relatively thin.

Condyle

The condyle comprises of head and neck. The condylar head or the articulating surface is covered by a thick avascular fibrous connective tissue containing fibroblasts. Below the avascular fibrous connective tissue is a layer comprising of prechondrocytes and chondrocytes. The chondrocytes lay down cartilage, which is transformed into bone by a process known as endochondral ossification. The fibrocartilage is present in condyle and articular eminence. Presence of fibrocartilage helps in adapting stress. In the aging condyle, there is less amount of cartilage and overloading may lead to degenerative joint diseases.

Capsule

The fibrous capsule (Fig. 4.3) is a loose envelope, which defines the anatomical and functional boundaries of the joint. Anteriorly and posteriorly, the capsule is loose, to allow mandibular movement. Medially and laterally, the capsule is firm, to stabilize the mandible during movement. The medial capsule is not as strong as the lateral capsule, which is reinforced by the lateral ligament.

1. **Anteriorly:** Capsule is attached approximately 4 mm anterior to the apex of the articular eminence.
2. **Posteriorly:** Capsule is attached to the anterior lip of the petrotympanic fissure.
3. **Superiorly:** Capsule is attached to the margins of the articular fossa.
4. **Inferiorly:** Capsule is attached to the neck of the condyle medially and laterally.
5. **Medially:** Capsule is short and merges into the periosteum below the medial pole of the condyle (Fig. 4.4).
6. **Laterally:** Capsule merges into the periosteum below the condylar neck (Fig. 4.4).

Ligaments

The TMJ is supported by lateral ligament (see Fig. 4.3) and two accessory ligaments (Fig. 4.5). The lateral ligament is present lateral to the capsule. It runs from the inferior border of zygomatic process of the temporal bone obliquely downwards, backwards to be inserted into the neck of the condyle. The two accessory ligaments that protect TMJ joint during wide excursions are stylomandibular ligament and sphenoman-dibular ligament. The stylomandi-bular ligament runs from the tip of the styloid process to the angle and posterior border of the mandible. In comparison, the sphenomandibular ligament runs from the greater wing of the sphenoid bone to the lingula of the mandibular ramus.

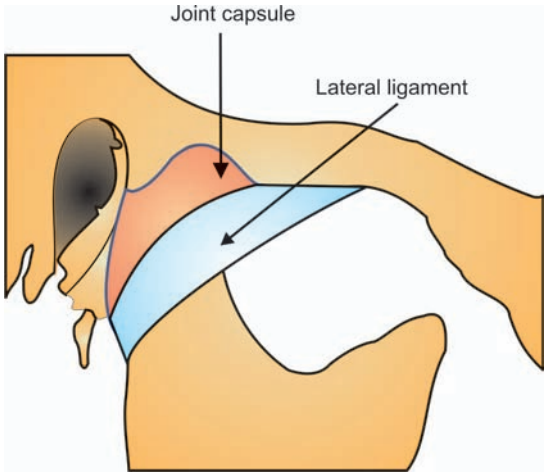

Fig. 4.3: Lateral ligament and capsule

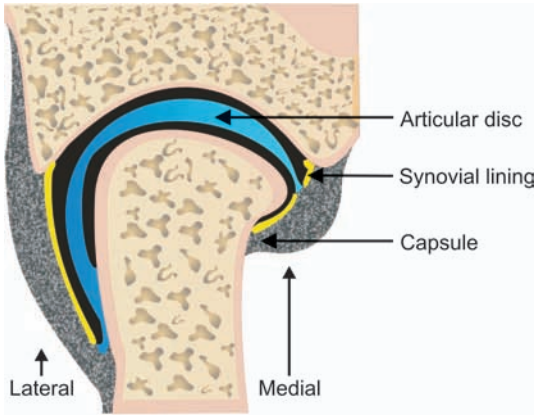

Fig. 4.4: Coronal section of temporomandibular joint

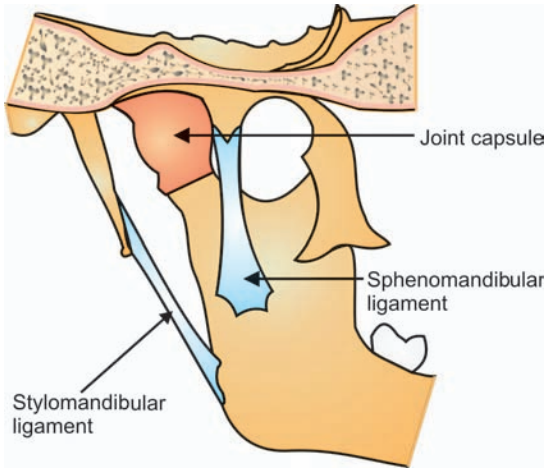

Fig. 4.5: Accessory ligaments

Synovial Lining

The capsule consists of two layers: outer fibrous layer and inner synovial lining. The synovial lining (Fig. 4.4) lines all the intra-articular structures except the articular eminence, articular fossa, articular disc, condyle, and the fibrocartilage. The symovial lining consists of two layers: The first layer is the *synovial intima*, which faces the joint space and consists of type A and type B cells (Table 4.1). The second layer is the *subintima*, which is a supportive layer and consists of loose fibrous connective tissue. The synovial subintima consists of extracellular matrix, which shows morphologic differences based on electron microscopic features. It is generally differentiated into three types: areolar (loose collagen), fibrous (dense collagen), and adipose (lipid globules). The capillaries that lie beneath the synovial intima are fenestrated suggestive of rapid exchange of water and solutes. In the deeper layers of the synovial subintimal tissue, substance P nerve fibres, calcitonin gene related peptide nerve fibers, and Vater-Pacini corpuscles are found.

Table 4.1: Cells of the synovial intima

Type A	Type B
• Bone marrow derived monocytes	• Arise from the mesenchyme of the original skeletal blastema
• Closely related to macrophages	• Closely related to fibroblasts
• Characterized by prominent Golgi apparatus	• Characterized by prominent rough endoplasmic reticulum
• Phagocytic function	• Secretory function

Synovial fluid: The synovial lining produces synovial fluid. In a healthy TMJ there is very little amount of synovial fluid. Increased amount of synovial fluid indicates joint pathology. The chemical composition of synovial fluid indicates that it is a dialysate of plasma. The synovial fluid consists of hyaluronic acid – protein complex with very few glycosaminoglycans (GAGs). The hyaluronic acid is responsible for slippery or viscous consistency of the fluid. The synovial fluid consists of a protein known as lubricin, which helps in lubrication of the joint. The synovial fluid reduces the friction between the articular surfaces by serving as a lubricant, provides nutrition to the non-vascularised tissue of the articular surfaces and the disc, and removes debris from the joint space.

Articular Disc

Articular disc should not be termed as meniscus as meniscus is semilunar shaped and disc is biconcave and rigid. The articular disc consists of dense avascular fibrous tissue. The articular disc is divided into anterior, intermediate, and posterior zone. The articular disc fits like a cap over the condyle. Its lower surface is concave and upper surface is convex. Medially and laterally, the disc is attached to the capsule (see Fig. 4.4). Anteriorly and posteriorly, the disc divides into superior and inferior lamellae. Anteriorly the disk splits into two lamellae: upper and lower lamellae (Fig. 4.6). The upper lamella is attached to the anterior edge of the articular eminence. The lower lamella is attached to the anterior surface of the condylar head. Between these two lamellae, the muscle fibres of the superior head of lateral pterygoid are inserted. Posteriorly the disk splits into two lamellae: upper and lower lamellae (the bilaminar region) (Fig. 4.6). The upper lamella gives way to loosely textured mass of tissue containing many blood vessels, nerves, fat, and elastic fibers. The loosely textured mass of tissue is attached to the capsule posteriorly and petrotympanic fissure superiorly. This loosely textured mass of tissue is known as retrodiscal pad. The lower lamella is attached to the neck of the condyle. The lower lamella limits the anterior movement of the disc, thus when it is damaged

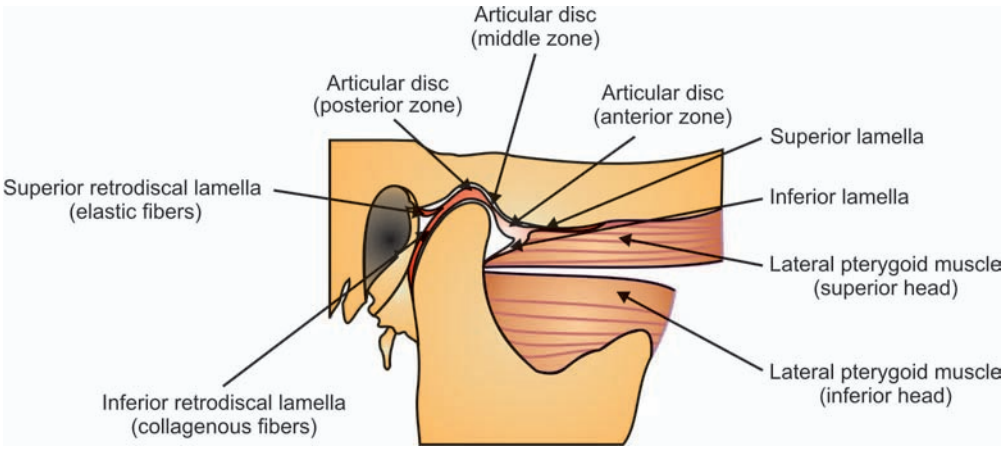

Fig. 4.6: Temporomandibular joint anatomy

the articular disc can translate anterior to condyle, resulting in disc displacement. When the mandible is at rest the ideal articular disc position in the articular fossa is with the posterior band at approximately 12 o'clock position. The articular disc divides the joint space into superior and inferior compartments, adapts to the articular surface thereby increasing the stability of the joint, protects the articular surface, acts as a shock absorber, and helps in joint movements.

Innervation of TMJ

The nerves that innervate the TMJ are auriculotemporal nerve, masseteric nerve, and the posterior deep temporal nerves. They are derived from the mandibular nerve after its passage through the foramen ovale, which is located medial to the articular eminence.

Auriculotemporal Nerve

The auriculotemporal nerve is a sensory nerve with autonomic nerve function. After it leaves the mandibular nerve, immediately below the skull base, it runs posteriorly and slightly downwards along the medial surface of the lateral pterygoid muscle. It then turns laterally crossing the posterior border of the condylar neck where it divides into several branches that innervate the capsule and disk attachments posteriorly, laterally and medially.

Masseteric Nerve

The masseteric nerve is a motor nerve, which innervates the anterior capsule and anterior disc attachment. After it leaves the mandibular nerve, it runs laterally along the medial border of the lateral pterygoid muscle, to emerge through the anterior part of the mandibular notch, behind the tendon of the temporalis muscle, to innervate the masseter muscle.

Posterior Deep Temporal Nerve

The posterior deep temporal nerve is a motor nerve, which innervates the anterior capsule and anterior disc attachment. After it leaves the mandibular nerve, it turns upwards and passes superior to the lateral pterygoid muscle to innervate the deep surface of the temporalis muscle.

Receptors

The TMJ contains four types of nerve receptors (Fig. 4.7) namely, Ruffini receptors, Golgi tendon organs, encapsulated Vater-Pacini corpuscles, and free nerve endings.

Receptors	Location	Function
Ruffini receptors	Capsule	Pressure (objects between the teeth)
Golgi tendon organs	Ligaments	Proprioceptors (mandibular position)
Vater-Pacini corpuscles	Capsule	Pressure (objects between the teeth)
Free nerve endings (nociceptors)	Capsule Retrodiscal tissue	Pain

Fig. 4.7: Temporomandibular joint receptors

TEMPOROMANDIBULAR JOINT PAIN

INTRODUCTION

Pain is the most common chief complaint in temporomandibular joint disorder. It is very difficult to evaluate because of individual differences in experience. Pain can demonstrate variety of qualities (Table 4.2). Each variety of pain is characteristically associated with pathology (Fig. 4.8).

Table 4.2: Varieties of qualities

• Piercing	• Aching
• Shooting	• Stinging
• Burning	• Squeezing
• Grinding	• Numbing
• Throbbing	• Itching
• Cramping	• Tingling

Varieties of pain	Associated with
Sharp and lacerating pain	Neuralgias
Shooting, burning, or sharp pain	Nerve entrapment
Deep or dull pain	Muscle pain
Aching pain	Inflammatory conditions
Throbbing pain	Vascular headaches

Fig. 4.8: Varities and association

DIAGNOSIS

When pain is present in the temporomandibular joint region, an accurate diagnosis is of prime importance. Any disorder that affects other synovial joints may also affect temporomandibular joint. Therefore, it is important to ask whether the patient has problems with any other joints or any known systemic disease.

HISTORY OF PAIN

The starting point in diagnosis of temporomandibular joint pain is to obtain an accurate description of the complaint. It should be first taken in the patients own words and then retold in technical language as indicated.

Description of Pain

Anatomic Location of Pain

The patients ability to locate the pain with accuracy has diagnostic value. The patients description of the location of pain identifies only the site of pain. It is the clinician's responsibility to determine whether that is the true source.

Intensity of Pain

The intensity of pain should be established by differentiating between mild and severe pain.

1. **Mild pain:** Patient describes the pain and does not display any physical reactions.
2. **Severe pain:** Patient describes the pain and displays physical reactions that are objectively evident to the clinician.

Mode of Onset

The mode of onset of pain has diagnostic value. The onset may be spontaneous or self-generated. It may be induced by yawning, chewing, drinking hot and cold fluids, or bending over. It may be accidentally triggered by minor superficial stimulation by touching the skin, lips, face, and tongue.

Quality of Pain (varieties)

The quality of pain should be classified according to how it makes the patient feel. When the pain has a stimulating or exciting effect on the patient it is classified as bright. When the pain has a depressing effect that causes patient to withdraw it is classified as dull.

Temporal Behavior

Temporal behavior can be classified as intermittent, continuous, and paroxysmal. If the pain comes and goes (pain-free intervals), it is classified as intermittent. Intermittent pain means that during the pain-free intervals the patient is comfortable. The intermittent pain-free intervals should not be confused with the effect of analgesics that induce periods of comfort by analgesia. If there are no pain-free intervals, it is classified as continuous or uninterrupted. Paroxysmal pain is characterized by sudden bursts of jabs, which may vary in intensity and duration. When the jabs occur frequently, the pain may become continuous.

Duration of Individual Pains

Momentary pain is expressed in seconds. Longer-lasting pains are classified in minutes, hours, or days. A pain that is continuous from one day to the next is said to be protracted.

Localization Behavior

The localization behavior of the pain should be included in its description. If the patient is able to define the pain to an exact anatomic location, it is classified as localized pain. If the patient is not able to define the pain to an exact anatomical location, it is classified as diffuse pain.

Effect on Functional Activities

The effect on functional activities should be observed and described. Common functions include movement of face, jaw, or tongue, mastication, deglutition, brushing of teeth, shaving, and washing the face.

Concomitant Symptoms

Any concomitant or accompanying symptoms should be described. The accompanying symptoms include:

1. **Hyperesthesia:** Increased sensitivity to stimulation
2. **Hypoesthesia:** Decreased sensitivity to stimulation
3. **Anesthesia:** Absence of all sensations
4. **Paresthesia:** Abnormal sensation
5. **Dysesthesia:** Unpleasant sensation

Temporomandibular Joint Pain

The origin of temporomandibular joint pain is not simple to diagnose. The most common source

of temporomandibular joint pain is due to temporomandibular joint problem. The principal challenge is to differentiate whether the pain is arthrogenous, myogenous, or referred pain.

Arthrogenous Pain

Aggravated by jaw functions (biting, chewing, talking, mouth opening, or lying down on the side).The temporomandibular joint is tender on palpation. Patient should be asked to point to the worst spot with one finger. If the worst spot is identified over the joint, it may be arthrogenous in origin

Myogenous Pain

Pain that is not aggravated by jaw functions indicates some other source of pain other than the joint. Patients with muscular disorders usually describe or point to diffuse areas often in the area of muscle distribution (temple, orbit, front of the head).

Referred Pain

Referred pain is described as the pain felt at an area that is innervated by a nerve, which does not mediate the primary pain. For e.g., patient may complain of pain in the temporomandibular joint area, but the source may be the salivary glands. Usually myogenous pain may be referred to the joint. This is especially true if the myofascial trigger points (Fig. 4.9) involve the strenocleidomastoid muscle, masseter, medial pterygoid, and lateral pterygoid muscles. However, referred pain from any source (such as the salivary glands) may be felt in the temporomandibular joint area.

Anesthetic Nerve Block

A good aid for establishing differential diagnosis is an anesthetic nerve block of the auriculotemporal nerve. If the pain is eliminated after the block, it is arthrogenous in origin. If the pain is not eliminated after the block, it is myogenous or referred in origin.

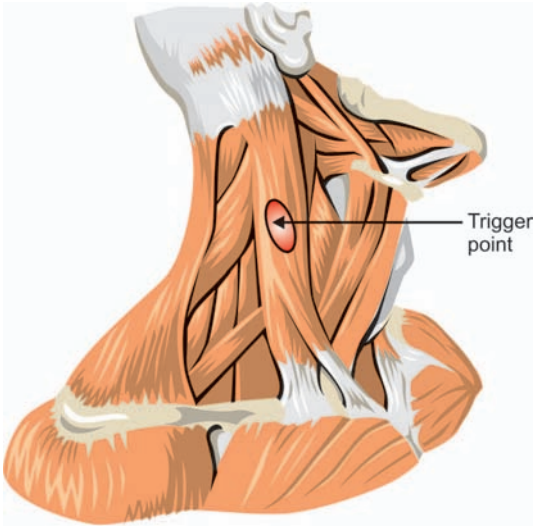

Fig. 4.9: Myofascial trigger point

Choice of Anesthetic

The long duration bupivacaine should not be used, as it is neurotoxic and may infiltrate to the central nervous system. Lignocaine or prilocaine is the choice of anesthetic.

Procedure

The needle should be directed from slightly behind and towards the neck of the condyle. The needle should meet the neck of the condyle. While keeping the needle in contact with the neck of condyle, the patient is instructed to open and close the mouth repeatedly within a small range of movement. By opening and closing the mouth repeatedly within a small range of movement, the clinician will know whether the needle is against movable condyle or not. The needle is then withdrawn a few millimeters to avoid injection into joint spaces. The goal of this procedure is to block the auriculotemporal nerve trunk behind the neck of the condyle.

Complications

As the facial nerve, runs adjacent to the joint, anesthesia can infiltrate and cause temporary

hemifacial anesthesia. Therefore, prior to the procedure the patient should be informed about temporary hemifacial anesthesia. If temporary hemifacial anesthesia occurs, the blink reflex on the ipsilateral side will be impaired and requires taping of the upper eyelid to protect the cornea.

Nerve Entrapment

The process by which the peripheral nerve is subjected to mechanical irritation by compression, rubbing, or traction is known as nerve entrapment. In the temporomandibular joint region, the auriculotemporal nerve, masseteric nerve, and posterior deep temporal nerves can be entrapped. Entrapment of these nerves gives rise to pain within the peripheral areas of the particular nerve distribution. For e.g., entrapment of the lingual nerve can produce symptoms related to the tongue such as pain, altered taste sensation, burning sensation, and numbness causing deviation in speech articulation.

TEMPOROMANDIBULAR JOINT SOUNDS

INTRODUCTION

Temporomandibular joint sounds (Table 4.3) indicate joint abnormality. Higher frequency of joint sounds is associated with more advanced disease. However, the absence of joint sounds does not exclude joint pathology.

CLICKING

Temporomandibular joint clicking refers to a distinct cracking or snapping sound. The prevalence of clicking is higher in women than in men and is higher during childhood and adolescence, and then decreases with age.

Conditions Associated with Clicking

Disc Displacement with Reduction

The most common cause of TMJ clicking is disc displacement with reduction. Clicking during mouth opening can occur early, intermediate, or late, depending on the advance of tissue damage, particularly of the posterior disc attachment. The more herniated and elongated the attachment,

Table 4.3: Varietis of TMJ sound

TMJ sound	Description
• Reciprocal click	Noise made on opening and closing from centric occlusion position that is reproducible on every opening and closing. Can be eliminated with anterior repositioning of jaw
• Reproducible opening click	Noise with every opening, no noise when closing
• Reproducible laterotrusive click	Noise with every full laterotrusive movement, no noise on opening
• Reproducible closing click	Noise with every closing, no noise when opening
• Nonreproducible click	Present on opening or in laterotrusion but not repeatable
• Crepitus (fine)	Fine grating noise suggestive of mild bone-on-bone contact
• Crepitus (coarse)	Coarse grating noise suggestive of gross bone-on-bone contact
• Popping	Distinctly audible sound on opening

the later the opening click will occur. Clicking during mouth closure usually takes places during the last third of closing movement and, in most instances, immediately before tooth contact.

Local Soft Tissue Thickenings

When the mandibular disc and condyle with a normal interrelationship pass a local thickening on the articulating surface, clicking can occur. Clicking then occurs after muscular strength has been sufficiently great to overcome the obstacle (local soft tissue thickenings). These thickenings are somewhere along the posterior slope of the articulating eminence.

Joint Hypermobility

In a normal joint immediately after maximum jaw opening the condylar head is located at the apex of the articular eminence. Clicking can arise when the mandibular condyle and articular disc with a normal interrelationship pass the apex of the articular eminence. The apex of the articular eminence can serve as an obstacle for the mandibular condyle and articular disc in hypermobile joints. When the muscular strength overcomes the obstacle (articular eminence), condylar velocity increases and, the condyle-disc assembly passes the apex of the articular eminence. Opening click arises at the end of mouth opening and the mandible deflects toward the contralateral side. In most cases, no sound occurs during jaw closing, but sometimes occurs at the very beginning of mouth closure.

Loose Intra-articular Bodies

Loose intra-articular bodies can have different origins. They can arise because of synovial chondromatosis, osteoarthrosis, and intra-articular fractures. All these conditions occur rarely, but can cause clicking in combination with crepitations.

Muscular Incoordination

The superior and inferior head of the lateral pterygoid muscle control the movements of the condylar head and disc. Disturbance in the function of this muscle can result in an incoordinated movement of the condylar head and disc during jaw movements, which in turn can produce clicking sounds.

Clinical Registration of Clicking

The presence or absence of clicking should be proved with a stethoscope. The clinician may listen to one joint at a time with a conventional stethoscope or may listen to both the joints at a time using double stethoscope. However, the use of a stethoscope to record joint sounds is unreliable. A false-negative diagnosis can result when the mandibular condyle slides off and on to the disc without any clicking.

Crepitations

Crepitations can be either fine or coarse. Fine crepitations are fine grating noises suggestive of mild bone-on-bone contact and coarse crepitations are coarse grating noises suggestive of gross bone-on-bone contact. Crepitations are more common in complete denture patients, and patients with loss of molar support. Crepitations can also occur in patients with osteoarthrosis, rheumatoid arthritis, and synovial chondromatosis.

RESEARCH DIAGNOSTIC CRITERIA—TMD CLINICAL EXAMINATION

Temporomandibular disorder (TMD) is a collective term embracing a number of clinical problems that involve the muscles of mastication, the temporomandibular joint, or both of these.

Examination of the articulatory system should be comprehensive enough to avoid missing any signs or symptoms yet simple enough for all practitioners to perform routinely on all patients.

The overall examination should include an assessment of pain, opening pattern, vertical range of movement and joint sounds.

The masticatory muscles and joint should be palpated, the common signs of bruxism should be noted, the patients headache experience should be discussed, and the occlusion carefully examined.

1. General directions for examination
2. Assessment of pain location
3. Opening pattern
4. Vertical range of movement
5. Joint sounds on vertical opening
6. Jaw excursions (lateral and protrusive)
7. Joint sounds on lateral and protrusive excursions
8. Muscle and joint palpation
   a. Extraoral muscles
   b. Temporomandibular joint
   c. Intraoral muscles

GENERAL DIRECTIONS FOR EXAMINATION

1. All questionnaire and examination items need to be completed unless the patient refuses or is unable to cooperate. In this case, write "PR" (patient refuses) in large block letters adjacent to the examination item and note why the patient refuses or cannot do item.
2. Measurements need to be conducted with the patients jaw muscles in a passive state.
3. The joints and muscles should not receive additional weight at anytime.
4. Millimeter measurements should be clearly recorded in single or double digits.
5. The patient should be sitting in the examination chair at approximately 90 degress to the examiner.
6. Examiner needs to wear gloves at all times.
7. Replacement prosthesis should not be removed from the patients mouth during the examination. However, biteplates and other appliances that do not replace teeth should be removed.
8. If the patient has a beard, a neck brace or any other potential physical barrier that may interfere with the muscle or TMJ palpation, indicate this.
9. The examination is most efficient if performed in the order mentioned above.

Examination

Assessment of Pain Location

1. At the beginning of the examination, the patient should be asked if he or she is in pain and the side and location of the pain noted.
2. If the patient indicates pain in the midline, it should be scored as both right and left sides painful.
3. If it is unclear whether the patient is indicating a joint or muscle, the examiner should press on the area as lightly as possible to help identify the correct site.
4. If the patient identifies joint pain but the examiner identifies the site as muscle, the examiners finding is the one that should be recorded.

Opening Pattern

1. Ask the patient to open the mouth as wide as he/she can even it is painful and close.
2. This initial opening puts the muscles in a functional state.
3. Next, the patient is asked to open the mouth three times with the opening pattern scored based on movement deviation.
4. Note that the examiner holds the lower lip during opening to reveal the lower teeth.
5. Be careful not to apply too much pressure or guidance.
6. There are four categories of opening pattern:
   a. Straight
   b. Deviation (right or left)
   c. Corrected deviation
   d. Other (If the deviation is jerky that does not fit any other category or of the patient has more than one opening pattern).

Vertical Range of Movement

If the patient is wearing a denture or partial and it is loose, it should be compressed against the ridge during the opening measurement.

Unassisted Mandibular Opening without Pain

Obtaining measurement

1. Ask the patient to place the mandible in a comfortable position.
2. Ask the patient to open the mouth as far as possible (unassisted), without feeling any pain.
3. In measuring unassisted mandibular opening without pain, the mm ruler should be placed at the incisal edge of the maxillary incisors with the specific tooth noted and with the ruler held vertically to the labioincisal edge of the opposing mandibular incisor.
4. If opening is less than 30 mm, the measurement should be repeated.

Maximum Unassisted Mandibular Opening

Obtaining measurement

1. Ask the patient to place the mandible in a comfortable position.
2. Ask the patient to open the mouth as wide as possible (unassisted), even if he/she feels pain.
3. In measuring maximum unassisted mandibular opening, the mm ruler should be placed at the incisal edge of the maxillary incisors with the specific tooth noted and with the ruler held vertically to the labioincisal edge of the opposing mandibular incisor.

Pain

1. Ask the patient if he/she felt any pain on maximum unassisted mandibular opening.
2. The location of pain is scored in two ways: muscle pain and joint pain.
3. Record muscle pain as "None" (0), "Right Side" (1), "Left Side" (2), or "Both" (3).
4. Also, record joint pain as "Present" (1) or "Absent" (0).
5. If the patient has no pain, circle "NA" (9) for location.
6. If the patient indicates a feeling of pressure or tightness, score as "None."

Maximum Assisted Mandibular Opening

Obtaining measurement

1. Ask the patient to place the mandible in a comfortable position.
2. Ask the patient to open the mouth as wide as possible, even if he/she feels pain.
3. After the subject has opened the mouth, in order to assess maximum assisted mandibular opening place your thumb on maxillary central incisors and cross your index finger over to the mandibular centrals.
4. This position gives you the advantage to force the patients mouth open wider.

5. Use moderate pressure and be careful not to push the mandible beyond the patients tolerance.
6. In measuring maximum assisted mandibular opening, the mm ruler should be placed at the incisal edge of the maxillary incisors with the specific tooth noted and with the ruler held vertically to the labioincisal edge of the opposing mandibular incisor.

Pain

1. Ask the patient if he/she felt any pain on maximum assisted mandibular opening.
2. Score pain locations as in maximum unassisted mandibular opening.
3. If the patient indicates a feeling of pressure or tightness, score as "None."

Joint Sounds on Vertical Opening

General Instructions

1. The temporomandibular joint sounds are measured by palpation during vertical opening and closing.
2. In this part of the examination, the object is to determine the presence or absence of specific joint sounds.
3. This is done by placing your fingers over the patients temporomandibular joint, anterior to the tragus of the ear.
4. Although a stethoscope may also be used to assess joint sounds, the stethoscope assessment is less reliable than the palpation method.
5. The patient is asked to repeat the opening and closing maneuver three times and report if sounds are present.
6. If so, the sounds are categorized as click, coarse crepitus, and fine crepitus and are scored separately for opening or closing.

Definition of Sounds

0 = *None*

1 = *Clicking:* Clicking is defined as a distinct sound, of brief and very limited duration, with a clear beginning and end, which usually sounds like a "click."

2 = *Coarse crepitus:* Coarse crepitus is continuous, over a longer period of jaw movement. It is not brief like a click or pop; the sound is not muffled; it is the noise of bone grinding against bone, or like a stone grinding against another stone.

3 = *Fine crepitus:* Fine crepitus is a fine grating sound that is continuous over a longer period of jaw movement on opening or closing. It is not brief like a click; the sound may make overlapping continuous sounds. It may be described as a rubbing or crackling sound on a rough surface.

Scoring of Clicking Sounds

Reproducible opening click: Click is considered reproducible if it occurs during two of three openings from maximum intercuspation.

Reproducible closing click: Click is considered reproducible if it occurs during two of three closings.

1. The measurements of reproducible opening and closing clicks are measured using an mm ruler.
2. With the millimeter ruler, measure the interincisal distance at which the first opening and closing clicks are reported / heard.
3. The mm ruler should be placed at the incisal edge of the maxillary incisors with the specific tooth noted and with the ruler held vertically to the labioincisal edge of the opposing mandibular incisor.

Reproducible reciprocal click

1. If a reproducible click is measured on both vertical opening and closing, ask the patient to protrude the mandible, and to open and close from this protruded position.
2. If the click is eliminated, can be eliminated from this protruded jaw position circle "Yes" (1)

3. If the click is not eliminated, can be eliminated from this protruded jaw position circle "No" (0).
4. If the patient lacks either a reproducible opening or closing click, circle "NA" (9).

Jaw Excursions (lateral and protrusive)

The next part of the examination assesses both the degree of excursion and pain on lateral and protrusive movement.

Right Lateral Excursion

Obtaining measurement

1. Ask the patient to open the mouth slightly and move the mandible as far as possible to the right, even if it is uncomfortable.
2. With the teeth slightly separated, use a millimeter ruler to measure from the labioincisal embrasure between the between the maxillary central incisors to the labioincisal embrasure of the mandibular central incisors.

Pain

1. Ask the patient if he/she felt any pain when moving the mandible towards the right side.
2. The location of pain is scored in two ways: muscle pain and joint pain.
3. Record muscle pain as "None" (0), "Right Side" (1), "Left Side" (2), or "Both" (3).
4. Also, record joint pain as "Present" (1) or "Absent" (0).
5. If the patient has no pain, circle "NA" (9).
6. If the patient indicates a feeling of pressure or tightness, score as "None."

Left Lateral Excursion

Obtaining measurement

1. Ask the patient to open the mouth slightly and move the mandible as far as possible to the left, even if it is uncomfortable.
2. Record this measurement in the same manner as right lateral excursion.

Pain

1. Ask the patient if he/she felt any pain when moving the mandible towards the left side.
2. Score pain locations as in right lateral excursion.
3. If the patient indicates a feeling of pressure or tightness, score as "None."

Protrusion

Obtaining measurement

1. Ask the patient to open the mouth slightly and protrude the mandible.
2. If the patient has a deep overbite, ask him/her to open wider so he/she can protrude without getting interference from the maxillary incisors.
3. Record this measurement in the same manner as right lateral excursion.

Pain

1. Ask the patient if he/she felt any pain when moving the mandible forwards.
2. Score pain locations as in right lateral excursion.
3. If the patient indicates a feeling of pressure or tightness, score as "None."

Joint Sounds on Lateral and Protrusive Excursions

1. Sounds on excursions are assessed in the manner similar to that for assessing sounds on vertical opening.
2. The fingers are placed over the joint and the patient is asked to perform lateral and protrusive excursions.

Muscle and Joint Palpation

General Instructions for Muscle and Joint Palpation for Tenderness

1. Examining the muscles and joint capsules for tenderness requires that you press on a specific site using the fingertips of the index finger only with standardized pressure, as

follows: palpations will be done with 2 lbs of pressure for extraoral muscles, 1 lb of pressure on the joints and intraoral muscles.
2. Palpate the muscles while using the opposite hand to provide stability to the head.
3. The subject's mandible should be in a resting position, without the teeth touching.
4. Palpate the muscles while they are in a passive state.
5. Ask the patient to lightly clench and relax the muscles, in order to identify and palpate correct muscle site.
6. Because the site of maximum tenderness may vary from patient to patient, it is important to press in multiple areas in the region specified to determine if tenderness exists.
7. Before beginning the palpations, say: "In the next part of the examination, we would like you to record whether you feel pain or pressure when I palpate or press on certain parts of your head and face."
8. Ask the subject to determine if the palpation hurts (painful) or if he/she just feels pressure. If it hurts, ask the subject to indicate if the pain is mild, moderate, or severe.
9. Record pressure as "No Pain."

Extraoral Muscles

Temporalis

Temporalis (posterior)

1. Ask the subject to clench and then relax to help identify muscle.
2. Palpate posterior fibers behind the ears to directly above the ears.

Temporalis (middle)

1. Ask the subject to clench and then relax to help identify muscle.
2. Palpate fibers in the depression about 2 cm lateral to the lateral border of the eyebrow.

Temporalis (anterior)

1. Ask the subject to clench and then relax to help identify muscle.
2. Palpate fibers over the infratemporal fossa, immediately above the zygomatic process.

Masseter

Origin of Masseter

1. Ask the subject to clench and then relax to help identify muscle.
2. Palpate the origin of the muscle beginning in the area 1 cm immediately in front of the TMJ and immediately below the zygomatic arch, and palpate anteriorly to the border of the muscle.

Body of the Masseter

1. Ask the subject to clench and then relax to help identify muscle.
2. Start just below the zygomatic process at the anterior border of the muscle.
3. Palpate from here down and back to the angle of the mandible across a surface area about two fingers wide.

Insertion of the Masseter

1. Ask the subject to clench and then relax to help identify muscle.
2. Palpate the area 1 cm superior and anterior to the angle of the mandible.

Posterior Mandibular Region

Posterior mandibular region (stylohyoid and posterior belly of digastric)

3. Ask the subject to tip the head back a little.
4. Locate the area between the insertion of the sternocleidomastoid muscle and the posterior border of the mandible.
5. Place finger so it is going medially and upwards (and not on the mandible).
6. Palpate the area immediately medial and posterior to the angle of the mandible.

Submandibular Region

Submandibular region (medial pterygoid, suprahyoid, and anterior belly of digastric)

1. Locate the site under the mandible at a point 2 cm anterior to the angle of the mandible.
2. Palpate superiorly, pulling toward the mandible.
3. If a subject has a lot of pain in this area, try to determine if the subject is reporting muscle or nodular pain.
4. If it is nodes, indicate on the exam form.

Temporomandibular Joint

Lateral Pole

1. Place index finger just anterior to the tragus of the ear and over the subject's temporomandibular joint. Ask the subject to open slightly until the examiner feels the lateral pole of the condyle translated forward.
2. Use 1 lb pressure on the side that is being palpated, supporting the head with the opposite hand.

Posterior Disc Attachment

1. This site can be palpated intrameatally.
2. Place tips of the right little finger into the subject's left external meatus and the tip of the left little finger into the subject's right external meatus.
3. Point the fingertips towards the examiner and ask subject to slightly open the mouth (or wide open if necessary) to make sure the joint movement is felt with the fingertips.
4. Place firm pressure on the right side and then the left side while the subject's teeth are completely together. (change examination gloves.)

Intraoral Muscles

Explain to the patient that you will now be palpating the inside of the mouth: ("Now I am going to palpate inside your mouth. While I do these palpations, I would like you to keep your jaw in a relaxed position.").

Lateral Pterygoid Area

1. Before palpating, make sure the fingernail of the index finger is trimmed to avoid false positives.
2. Ask the subject to open the mouth and move the jaw to the side that is being examined. ("Move your jaw towards this hand.").
3. Place the index finger on lateral side of alveolar ridge above the right maxillary molars.
4. Move finger distally, upward, and medial to palpate.
5. If the index finger is too large, use the little finger (5th digit).

Tendon of Temporalis

1. After completing, the lateral pterygoid, rotate your index finger laterally near the coronoid process, ask the subject to open slightly, and move your index finger up the anterior ridge of the coronoid process
2. Palpate on the most superior aspect of the process.

RESEARCH DIAGNOSTIC CRITERIA—TMD EXAMINATION FORM

Do you have pain on the right side of your face, the left side, or both sides?

1. None……0
2. Right ……...1
3. Left …….2
4. Both…….3

Could you point to the areas where you feel pain?

Right

1. None……0
2. Jaw Joint…..1
3. Muscles……2
4. Both…….3

Left

1. None……0
2. Jaw joint…..1
3. Muscles……2
4. Both…….3

Opening Pattern

1. Straight 0
2. Right lateral deviation (uncorrected 1
3. Right corrected (“S”) deviation 2
4. Left lateral deviation (uncorrected) 3
5. Left corrected (“S”) deviation 4
6. Other 5
7. Type (specify) .....

Vertical Range of Movement (maxillary incisor used)

1. Unassisted mandibular opening without pain ____ mm
2. Maximum unassisted mandibular opening ____ mm
3. Maximum assisted mandibular opening ____ mm

Muscle pain				Joint pain		
None	Right	Left	Both	Present	Absent	NA
0	1	2	3	1	0	9
0	1	2	3	1	0	9

Joint Sounds

	Right	Left
Opening		
None	0	0
Click	1	1
Coarse crepitus	2	2
Fine crepitus	3	3

Measurement of reproducible opening click ____ mm ____ mm

	Right	Left
Closing		
None	0	0
Click	1	1
Coarse crepitus	2	2
Fine crepitus	3	3

Measurement of reproducible closing click ____ mm ____ mm.

Reproducible reciprocal click eliminated on protrusive opening

	Right	Left
No	0	0
Yes	1	1
NA	9	9

Excursions

1. Right lateral excursion ____ mm
2. Left lateral excursion ____ mm
3. Protrusion ____ mm

Muscle pain				Joint pain		
None	Right	Left	Both	Present	Absent	NA
0	1	2	3	1	0	9
0	1	2	3	1	0	9

Joint Sounds on Excursions

Right sounds

	None	Click	Coarse crepitus	Fine crepitus
Excursion right	0	1	2	3
Excursion left	0	1	2	3
Protrusion	0	1	2	3

Left sounds

	None	Click	Coarse crepitus	Fine crepitus
Excursion right	0	1	2	3
Excursion left	0	1	2	3
Protrusion	0	1	2	3

Muscle and Joint Palpation

The examiner will be palpating (touching) different areas of your face, head, and neck. We would like you to indicate if you do not feel pain or just feel pressure (0), or pain (1-3). Please rate how much pain you feel for each of the palpations according to the scale below. Circle the number that corresponds to the amount of pain you feel. We would like you to make a separate rating for both the right and left palpations.

0 = No Pain/pressure Only
1 = Mild Pain
2 = Moderate pain
3 = Severe pain

Extraoral Muscle Palpation

	Right				Left			
Temporalis								
Temporalis (posterior) "Back of temple"	0	1	2	3	0	1	2	3
Temporalis (posterior) "Back of temple"	0	1	2	3	0	1	2	3
Temporalis (middle) "Middle of temple"	0	1	2	3	0	1	2	3
Temporalis (anterior) "Front of temple"	0	1	2	3	0	1	2	3
Masseter								
Masseter (origin) "Cheek/under cheekbone"	0	1	2	3	0	1	2	3
Masseter (body) "Cheek/side of face"	0	1	2	3	0	1	2	3
Masseter (insertion) "Cheek/jaw line"	0	1	2	3	0	1	2	3
Posterior mandibular region (stylohyoid / posterior digastric region) "Jaw / throat region"	0	1	2	3	0	1	2	3
Submandibular region (medial pterygoid / suprahyoid/ anterior digastric region) "Under chin"	0	1	2	3	0	1	2	3

Joint Palpation

	Right				Left			
Lateral Pole "Outside"	0	1	2	3	0	1	2	3
Posterior attachment "Inside ear"	0	1	2	3	0	1	2	3

Intraoral Muscle Palpation

	Right				Left			
Lateral pterygoid area "Behind upper molars"	0	1	2	3	0	1	2	3
Tendon of temporalis "Tendon"	0	1	2	3	0	1	2	3

INTERNAL DERANGEMENT

In 1814, the term internal derangement was introduced by Hey as a general orthopedic term for a localized mechanical fault in a joint. Internal derangement is the most common temporomandibular joint disorder, which is characterized by a progressive displacement of disc relative to the condyle.

According to the consensus meeting held by the International Association of Oral and Maxillofacial Surgeons (IAOMS) in Buenos Aires 1992 regarding TMJ-surgery, internal derangement is defined as a localized mechanical fault of the joint which interferes with its smooth action. In simpler terms, internal derangement may be defined as the loss of spatial relationship within the temporomandibular joint in which there is displacement of the disc (Fig. 4.10) from its normal anatomical and functional relationship with the mandibular condyle and the articular fossa.

ETIOLOGY

The three causes of internal derangement are macrotrauma, microtrauma, and occlusal factors.

Macrotrauma

Macrotrauma to the temporomandibular joint can occur because of fractures, joint contusion, whiplash injuries or iatrogenic injuries during dental treatment. These conditions produce bruising or joint tissue laceration that may lead to an impaired function and eventually to an internal derangement.

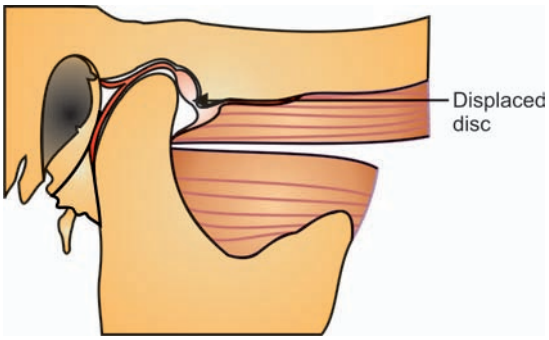

Fig. 4.10: Internal derangement

Microtrauma

Microtrauma can occur from repetitive behaviors such as chronic clenching, bruxism, atypical chewing habits and nail biting.

Occlusal Factors

Occlusal factors such as class II, class II division II malocclusions, loss of molar support and retentive phase in orthodontic treatment that may deflect the condyle posteriorly have also been suggested as etiological factors.

CLINICAL STAGING

The most common TMJ disorder is the internal derangement, which is characterized by a progressive anterior disc displacement relative to the condyle. Traditionally, internal derangement of the TMJ may be classified into four consecutive clinical stages:

1. Stage I as disc displacement with reduction
2. Stage II as disc displacement with reduction and transient locking
3. Stage III as disc displacement without reduction (closed lock)
4. Stage IV as disc displacement without reduction and with perforation of the disc or posterior attachment tissue (degenerative joint disease)

Stage I

Disc displacement with reduction is the Stage I of disc displacement. In Stage I, the displaced disc

returns to normal position on mouth opening. Stage I is characterized by reciprocal clicking of the TMJ on opening and closing. The opening click occurs when the condyle slides over the posterior band of the disc. The closing click reflects a reversal of this process, with the condyle moving under the posterior band of the disc until it snaps off the disc and onto the posterior disc attachment. Disc displacement with reduction can occur without clicking. Therefore, the absence of joint sounds does not indicate that the joint is normal. The clinical hallmark of disc displacement with reduction is limited mouth opening, usually accompanied by deviation of the mandible to the affected side, until a click (reduction) occurs. After the click, the mandible returns to midline position and the patient is able to open the mouth fully.

Stage II

Stage II features all the characteristics of Stage I, plus additional episodes of transient locking or joint locking, which can last for various lengths of time. Stage II begins when the disc is lodged anteriorly in relation to the condyle, thereby blocking translation and causing clinical locking. Patients may describe it as "hitting an obstruction" when opening is attempted. The "obstruction" may disappear spontaneously or the patient may be able to manipulate the mandible beyond the interference. Repetitive locking and opening creates strain in the posterior disc attachment, resulting in laxity.

Stage III

Stage III is characterized by closed-lock (disc displacement without reduction).The clicking noise disappears and the patient complains of joint pain and limited mouth opening. Clinical examination reveals preauricular tenderness, deviation of the mandible to the affected side and mouth opening less than 30 mm. Magnetic resonance imaging shows anterior disc displacement in both centric occlusion and maximal mouth open positions. As the condition progresses, the condyle may steadily push the disc forward to achieve almost normal ranges of mouth opening, in spite of the presence of a non-reducing disc.

Stage IV

As the condyle steadily pushes the disc forward the posterior disc attachment slowly loses its elasticity, and the patient begins to regain some of the lost range of motion (translation). The posterior disc attachment gradually remodels with deposition of fibrous connective tissue before it succumbs to thinning and perforation due to continuous stretching. Disk perforation and bone-to-bone contact will elicit coarse crepitus upon opening and closing. Clinically, osteoarthrosis may be diagnosed because the remodelling often occurs unilaterally, the symptoms appear to worsen as the day goes on, and radiographic evidence is frequent (e.g., flattening, sclerosis, osteophytes, erosion).

CLINICAL TEST TO DIAGNOSE DISC DISPLACEMENT

In order to diagnose disc displacement with reduction the patient is instructed to clench the teeth in an intercuspal position. In a joint with a reducing disc, the disc then becomes displaced. The patient is instructed to open the mouth until clicking occurs, indicating reduction of the disc, and from there to protrude the mandible and perform all jaw movements (opening, closing, and lateral excursion). The patient is then is instructed to let the mandible return to the normal intercuspal position. If clicking reoccurs when the patient opens the mouth, the diagnosis is disc displacement.

Treatment

A majority of the patients with symptomatic internal derangement can be successfully treated with non-surgical methods but in approximately 5%, surgery is performed. According to Okeson, the four types of treatment that should be considered for patients with painful internal derangement are counseling, physical therapy, pharmacological therapy, and occlusal therapy. Should these methods prove unsuccessful, they are often followed by surgical methods such as meniscectomy, disc repositioning procedures, condylotomy, arthroscopy, and arthrocentesis.

Counseling

Counseling includes patient education and reassurance and is an important part of the management. Patient education is important in order to modify the patients behavior. It includes a brief description of the disorder, and an apt discussion about the treatment. A well-informed patient could play a major role in the treatment since the disorder is of biomechanical nature and therefore the patient should be instructed to eat soft food in order to decrease joint loading. Patient reassurance requires an understanding dentist. The patients should be told that their problem is commonly found in the population; that it is a benign disorder; that it is not life threatening; and has a very good prognosis. Such information, when conveyed by a confident dentist has a powerful effect on the patients concern and anxiety. Therefore, reassurance may be the only treatment necessary for many patients.

Physical Therapy

The aim of physical therapy is to reduce muscle-joint pain and to improve the joint function. Physical therapy may include application of moist heat and coolant therapy in form of hot moist towels, ice cubes, and different vapo-coolant spray containing ethylchloride or fluoromethane. Other commonly prescribed methods include transcutaneous electric nerve stimulation (TENS), ultrasound, soft laser, and acupuncture. In order to avoid hypomobility and muscle atrophy because of pain the patient should be instructed to perform different jaw exercises to improve muscular coordination, relax tense muscles, increase the range of motion of the mandible, and increase muscular strength.

To achieve a favorable effect, the standard program of jaw exercises must be performed for 2 to 3 minutes at least 2 to 3 times a day, for a minimum period of 2 to 3 months. The various jaw exercises are as follows:

1. Maximum mouth opening without resistance (Fig. 4.11)
2. Mouth opening against resistance (Fig. 4.12)
3. Mouth closing against resistance (Fig. 4.13)
4. Excursion of the mandible to the right (Fig. 4.14)
5. Excursion of the mandible to the right against resistance (Fig. 4.15)
6. Excursion of the mandible to the left (Fig. 4.16)
7. Excursion of the mandible to the left against resistance (Fig. 4.17)
8. Protrusion of the mandible (Fig. 4.18)
9. Protrusion of the mandible against resistance (Fig. 4.19)
10. Stretching exercise (Fig. 4.20)

Fig. 4.11: Maximum mouth opening without resistance

Fig. 4.12: Mouth opening against resistance

Fig. 4.15: Excursion of the mandible to the right against resistance

Fig. 4.13: Mouth closing against resistance

Fig. 4.16: Excursion of the mandible to the left

Fig. 4.14: Excursion of the mandible to the right

Fig. 4.17: Excursion of the mandible to the left against resistance

Fig. 4.18: Protrusion of the mandible

Fig. 4.19: Protrusion of the mandible against resistance

Fig. 4.20: Stretching exercise

If extra-force is needed or if the patient cannot generate the necessary amount of force to open the mouth, special devices such as therabite are available to assist the patient in performing stretching exercise.

Pharmacological Therapy

Since pain is the most common symptom in temporomandibular joint disorder or TMD disorder, pain relief is an important part of treatment of TMD. The most common medication used is nonsteroidal anti-inflammatory drugs (NSAID). When muscle tension is a problem, a muscle relaxant and anti-anxiety medications can be prescribed. Intra-articular injections of corticosteroids (8 injections a year with 6 to 8 weeks interval) and hyaluronic acid may be administered. Intramuscular injections of local anesthetics into tender areas can relieve muscular pain.

Occlusal Therapy

There are mainly two types of occlusal appliances for the treatment of internal derangement. The stabilization appliance is prescribed more frequently than any other occlusal appliance. It is also known as full-coverage splint, flat splint, and occlusal bite plane. The stabilization appliance reduces muscular hyperactivity. It covers all teeth as well as areas without teeth and gets its retention by letting the acrylic just pass the prominence line of the teeth. In most patients, a positive treatment effect can be achieved by wearing the appliance only at night.

The other occlusal appliance for the treatment of internal derangement is the mandibular repositioning appliance. It is indicated for patients with only disc displacement with reduction. The mandibular repositioning appliance puts the mandible in a forward position so that the disc is recaptured to a correct anatomical position.

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Chapter

5

Tobacco, Areca Nut and Alcohol

INTRODUCTION

Tobacco *(Nicotiana tabacum)* is a member of the Solanaceae family (Fig. 5.1). The generic name of the tobacco plant, *Nicotiana*, is derived from the name of the French Ambassador to Portugal, Jean Nicot. Jean Nicot, introduced tobacco into the French court in 1560 for medicinal purposes. The tobacco leaves contain nicotine, a plant alkaloid. Tobacco is native of North America. Later, the plant came to be known by the name of the device, as "tobacco." The word tobacco was originally used to denote a "Y" shaped piece of cone or pipe called "tobago" or "tobaca" that was used by Mexican-Indians. Mexican-Indians used tobacco in number of ways:

1. Chewed the leaves to relieve hunger and thirst
2. Inhaled powdered tobacco (snuff) to clear the nasal passage
3. Smoked rolled up tobacco leaves, to relieve fatigue

CHEMICALS IN TOBACCO

Cigarette smoke contains over 4000 chemicals. At least 50 of the chemicals in tobacco smoke are known to cause cancer of the lung, throat, mouth, bladder and kidneys. About 23 chemicals that cause tumors have been isolated and identified in smokeless tobacco.

Fig. 5.1: *Nicotiana* tabacum

Nicotine

The most biologically active agent is the alkaloid, nicotine. Nicotine is a colorless, very hygroscopic, volatile oily liquid that gives tobacco its smell. It turns brown when exposed to air or light. Its formula is $C_{10}H_{14}N_2$ and molecular weight is

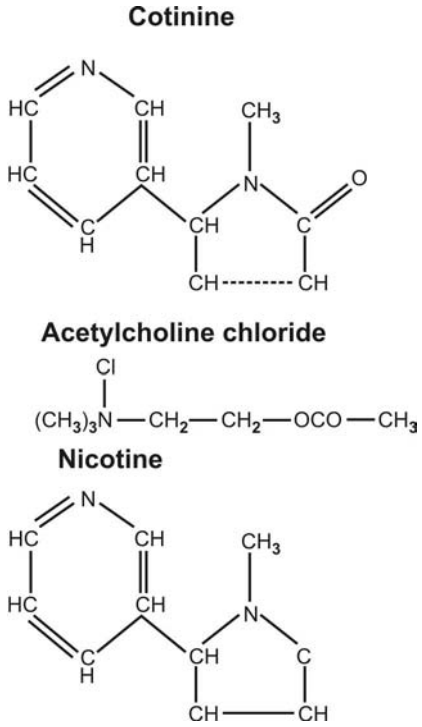

Fig. 5.2: Structures of nicotine, cotinine and acetylcholine chloride

162.23 (Fig. 5.2). Free nicotine is highly lipid soluble and hence can easily penetrate into tissues and cells, where it is readily absorbed. The absorbed nicotine in the blood reaches and accumulates in the brain within minutes, and exerts its psychological and pharmacological effects. It also enters various tissues, particularly the liver, where it is metabolized into cotinine and nicotine-N-oxide. Both these metabolites are biologically inactive. Cotinine is a useful indicator of all kinds of smoking, including passive smoking. Nicotine leaves the tissues rapidly and is excreted in the urine. Nicotine absorbed from chewing tobacco, passes through the liver first, where it is partly metabolized into inactive substances, and then reaches the blood stream. It is generally less active and less harmful than the nicotine present in the cigarette smoke, which is absorbed through the lungs and passes directly into the blood stream without being first inactivated in the liver.

Biologically nicotine resembles the neurotransmitter acetylcholine. Nicotine can combine with acetylcholine receptors in the body. Biological effects are largely due to this resemblance. Nicotine can act as a stimulant or as a depressant, depending upon the dosage. In low doses, it acts like a stimulating agent, just like acetylcholine, allowing impulses to pass through the nerves. In large doses, it combines and floods all receptors, blocking the passage of all nerve impulses. An overdose of nicotine (60 mg or more) causes a complete arrest of respiration.

Biological Effects of Nicotine

1. Increases the motility of gastrointestinal tract, followed by decrease in motility resulting in constipation
2. Nicotine initially increases and then depresses the salivary and bronchial secretion
3. Stimulates the adrenal medulla and increases the release of catecholamines, which in turn causes tachycardia and increase in blood pressure
4. In small doses, nicotine relieves anxiety, produces exhilaration, and suppressing anger.

Carcinogenic Agents

A variety of carcinogens are found in tobacco. They include volatile aldehydes, volatile N-nitrosamines, radioactive isotopes, and other toxic chemicals.

Volatile Aldehydes

1. Formaldehyde
2. Acetaldehyde
3. Crotonaldehyde

Volatile N-nitrosamines

The tobacco specific volatile N-nitrosamines are derivatives of alkaloids (nicotine, nornicotine, anabasine, and antabine). The alkaloids undergo nitrosation in the saliva, by using nitrites in the saliva and yield volatile N-nitrosamines (carcinogens). Nicotine gives rise to three potent carcinogens (Fig. 5.3). Of the three NNK is the most potent. The induction of oral cancers by NNN is considerably accelerated by the presence of HSV-1 and HSV-2, which act as cocarcinogens.

1. N-nitrosonornicotine (NNN)
2. 4-(N-nitrosomethlyamino)-1-(3-pyridyl) butanone (NNK)
3. 4-(N-nitrosomethlyamino)-1-(3-pyridyl) – 1-butanol (NNAL)

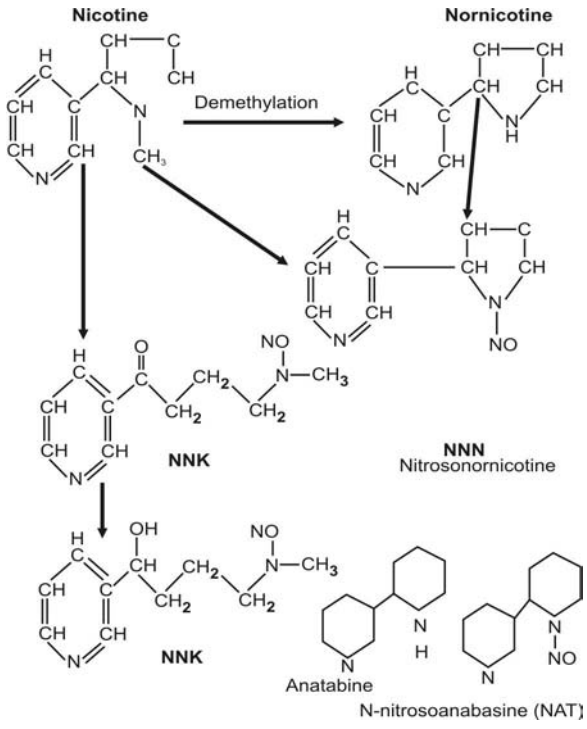

Fig. 5.3: Formation of N-nitrosamines from tobacco alkaloids

Radioactive Isotopes

1. Polonium–210
2. Uranium–235 and 238

Other Chemicals in Cigarette Smoke

1. Carbon monoxide
2. Carbon dioxide
3. Carbonyl sulfide
4. Benzene
5. Toluene
6. Acrolein
7. Acetone
8. Pyridine
9. Hydrogen cyanide
10. Nitrogen oxides
11. Benz (a) anthracene
12. Benzo (a) pyrene
13. Cholesterol
14. Phenol
15. Cadmium
16. Nickel
17. Zinc
18. Benzoic acid

Tobacco Habits

Around 1600 A.D. Portuguese traders brought tobacco, the pipe, and the cigar, into India. Tobacco habits in India are practiced in various different forms (Fig. 5.4) and (Fig. 5.5). Many of the habits are specific to certain areas of India. India is now the third largest producer of tobacco in the world, after China and the U.S.A.

Tobacco Habits—Smoking

1. *Bidi*
2. *Cigarette*
3. *Cigar*
4. *Chutta*
5. *Cheroot*
6. *Chilum*
7. *Dhumti*

States	Habits
Andhra Pradesh	Reverse chutta smoking
Tamil Nadu	Cigar
Kerala	*Cheroot*
Karnataka	*Dhumti*
Maharashtra	Cigarette
Gujarat	*Hookli*
Madhya Pradesh	*Bidi*
Bihar	*Hookah*
Orissa	*Chutta*
Uttar Pradesh	*Chilum*

Fig. 5.4: Smoking habits in India

States	Habits
Andhra Pradesh	*Supari*
Tamil Nadu	Seeval snuff
Kerala	Raw tobacco
Karnataka	Betel quid with tobacco
Maharashtra	*Mishri and khaini*
Gujarat	*Bajjar and mawa*
Madhya Pradesh	*Gutkha*
Bihar	*Gudhaku*
Uttar Pradesh	*Mainpuri tobacco and zarda*
Assam	*Bura taamool*

Fig. 5.5: Smoking habits in India

8. *Hookah*
9. *Hookli*
10. Reverse *chutta* smoking
11. Reverse *dhumti*

Tobacco Habits—Smokeless

1. Betel quid (pan) with tobacco
2. *Bajjar*
3. Creamy snuff
4. *Gudhaku*
5. *Gutkha*
6. *Khaini* (tobacco-lime preparation)
7. Mainpuri tobacco
8. *Mawa*
9. *Mishri*
10. Red tooth powder (*lal dant manjan*)

The Health Risks of Tobacco Smoking (Fig. 5.6)

1. Angina pectoris
2. Asthma
3. Atherosclerosis
4. Bladder cancer
5. Cancer of the larynx
6. Cancer of the lungs
7. Cancer of the oesophagus
8. Cervical cancer
9. Chronic bronchitis
10. Emphysema
11. Hypertension
12. Impotency
13. Low birth weight baby
14. Myocardial infarction
15. Peptic ulcer
16. Pancreatic cancer
17. Stroke

Tobacco and Oral Health

1. Oral cancer
2. Precancerous lesions
    a. Preleukoplakia
    b. Leukoplakia
    c. Erythroplakia
    d. Smoker's palate
3. Tobacco-induced oral mucosal conditions
    a. Leukoedema
    b. Palatal erythema
    c. Tobacco-lime user's lesion
    d. Pan encrustation
    e. Snuff dipper lesion
    f. Smoker's melanosis
4. Tobacco-associated effects on the teeth and supporting tissues
    a. Premature tooth loss

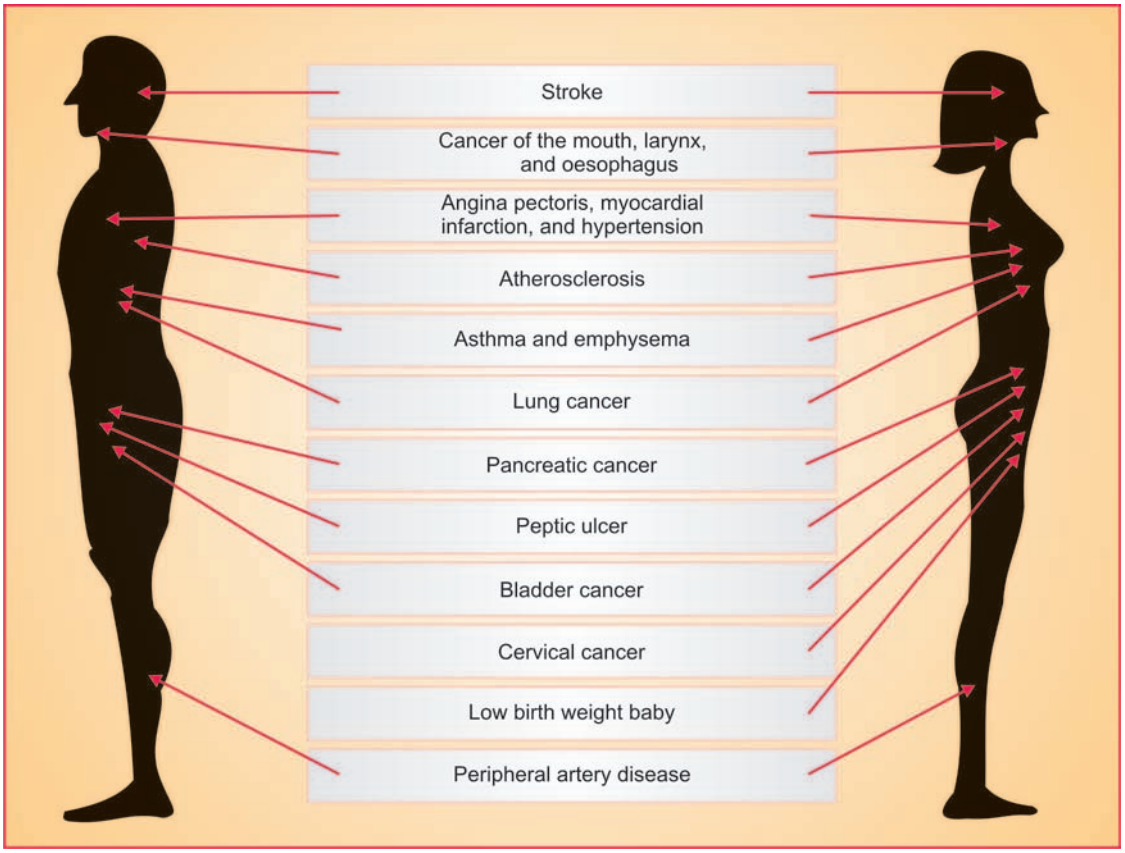

Fig. 5.6: The health risks of tobacco smoking

b. Staining
c. Abrasion
d. Attrition
e. Periodontal diseases
f. Acute necrotizing ulcerative gingivitis

5. Other tobacco associated oral conditions
   a. Calculus
   b. Halitosis
   c. Chronic hyperplastic candidiasis
   d. Median rhomboid glossitis
   e. Black hairy tongue

Smoking Cessation

The most important step that smokers need to take in order to improve their oral health and minimize the risk of oral cancer is to stop smoking. Dentists can play a vital role in smoking cessation. Evidence indicates that smoking cessation interventions are both effective and cost-effective. Smoking cessation interventions result in significant health gain and, in the long term, reduce smoking-related health-care costs.

Giving up smoking is a difficult process made up of a series of steps rather than one event and dentists can help smokers at the varying stages in the quitting process. Of utmost importance, however, is to let smokers know that it is never too late to stop smoking and that the sooner they do, the greater the benefits will be to their long-term health.

The Four As

There are four essential features of smoking cessation advice. These steps are recommended in the recently published evidence based *Smoking Cessation Guidelines.*

1. Ask about smoking at every opportunity
2. Advice all smokers to stop
3. Assist the smokers to stop
4. Arrange follow-up

Ask

All patients should have their smoking status established and kept as up-to-date as possible, for example, following every visit. At the very least, this record should cover whether the patient is a smoker, non-smoker, or recent ex-smoker, and note any current interest in stopping. Interest in stopping can be assessed with an open-ended question such as "Have you ever tried to stop?" This can be followed by "Are you interested at all in stopping now?"

Other types of questions can be asked:

1. How many cigarettes do you smoke?
2. How long have you been smoking?
3. When do you smoke?
4. Have you ever tried to stop smoking?

From these questions, it is easy to identify what might help the smoker make the decision to stop smoking.

Advice

Every smoker must be told of the value that stopping smoking will have for them and of the risks to health that exist in continuing. Because the needs and reasons for wanting to stop smoking will be different for every smoker, it is important to examine each individual situation and give plain, precise, and personalized advice to them. This can include recommending aids to stopping smoking such as using Nicotine Replacement Therapy (NRT).

Reasons for quitting will obviously vary for different groups of smokers but might include the following:

1. **Pregnant women:** Increased risk of low birth-weight and fetal death
2. **Long-term smokers:** Increased risk of heart disease, cancer, and stroke
3. **New smokers:** Easier to stop now than later
4. **Any smoker:** Save money and feel healthier

Assist

If the smoker would like to stop, help should be offered. A few key points can be covered with the smoker in 5-10 minutes.

1. Set a date to quit smoking; stop smoking completely on that day
2. Review past experience: what helped, what hindered?
3. Provide self-help literature
4. Discuss the health benefits of quitting
5. Tell family and friends to prepare the environment (discard cigarettes)

Arrange

Arranging a follow-up is very important. Studies indicate that successful quit rates are high when follow-up contact is routinely made with interested patients. Patients should be seen ideally 1-2 weeks after their quit date. Most smokers make several attempts to stop before finally succeeding (the average is around 3-4 attempts), so relapse is a normal part of the process. To help smokers overcome nicotine cravings, dentists can recommend the following the "Four Ds," aimed at reducing the urge to smoke:

1. **Delay:** Do not open a pack or light a cigarette. After a few minutes, the urge to smoke weakens and your resolve to quit will come back
2. **Deep breaths:** Take three deep, slow breaths in and out

3. **Drink water:** Sip it slowly and enjoy the taste
4. **Do something else:** Take your mind off smoking by doing some exercise, listening to music or talking to a friend

Aids to Cessation

Some people find it easier than others to stop smoking, and the degree of difficulty is not always related to tobacco consumption. Factors such as maturity, the ability to cope with stress or confidence of success are equally important.

Nicotine Replacement Therapy (NRT)

Nicotine replacement therapy (NRT) is the most widely used pharmaceutical aid to assist individuals in their attempts to stop smoking. Nicotine replacement therapy is available in the form of a gum, patch, nasal spray, and inhalator. Nicotine replacement therapy is contraindicated in patients with diabetes mellitus, hyperthyroidism, or pheochromocytoma, renal or hepatic insufficiency, asthma, peptic ulcers, contact dermatitis, generalized skin disorders, nicotine allergy, depression, pregnancy, breast-feeding, temporomandibular joint disease, and oral inflammation.

Conclusion

Stopping smoking prolongs life regardless of the age at which a person stops.

A smoker's life span is shortened by about five minutes for each cigarette smoked. On average, those killed by smoking have lost 10 to 15 years of life.

ARECA NUT

The areca nut resembles tobacco in some ways. Like tobacco, it also contains many alkaloids, of which the most important is arecoline. These alkaloids like nicotine have stimulating effects on the human body. They are also probably addictive, though to a lesser degree than nicotine. The nitrosation of areca nut alkaloids yields carcinogenic N-nitrosamines, the most active among them being 3-(methylnitrosamino) propionitrile (MNPN). The areca nut is composed of carbohydrates (50-75 %), proteins (5-8 %), fats (14%), red tannins (15 %), alkaloids, and other nitrogenous bases such as choline. The alkaloids present in areca nut are arecoline, arecaidine, guvacoline, and guvacine. Arecaidine and guvacoline are isomers, containing one methyl group less than arecoline. Both the methyl groups of arecoline are absent in guvacine (Fig. 5.7). Among these alkaloids, arecoline is by far the most important, occuring to the extent of 0.5-0.7 % in areca nut. Its molecular formula is $C_8H_{13}NO_2$, and molecular weight is 155.19. Arecoline is an oily liquid; with a boiling point of 209°C and a strong base, which is freely miscible with water, alcohol, and ether. Arecoline mimics the action of acetylcholine, and stimulates both the central and peripheral nervous system. The euphoric effect of areca nut is due to arecoline. The cytotoxic properties of arecoline

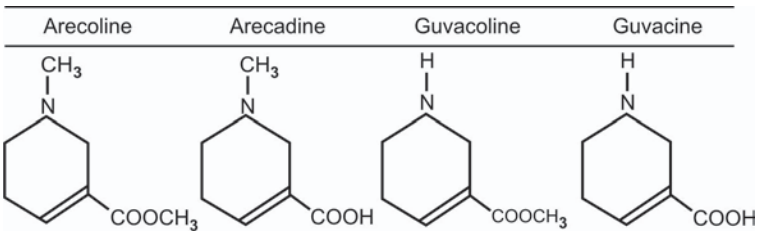

Fig. 5.7: Areca nut alkaloids

and guvacoline are due to the presence of a methylester group. The lower polarity and lower degree of ionization of arecoline and guvacoline may facilitate their passage over biological membranes.

Nitrosation of the areca nut alkaloids takes place in the mouth through the nitrites in the saliva. Nitrosation of arecoline yields four N-nitroso compounds (Fig. 5.8), N-nitrosoguvacoline (NG), N-nitrosoguvacine (NGC), 3-(methylnitrosamino) propionaldehyde (MNPA), and 3-(methylnitrosamino) propionitrile (MNPN). Among these N-nitroso compounds, MNPN and MNPA are highly genotoxic and carcinogenic. Areca nut produced in India, can be classified broadly under three heads:

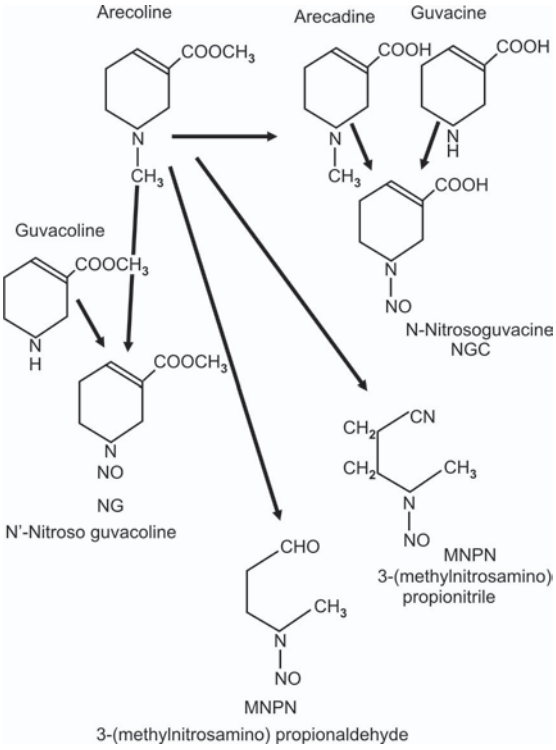

Fig. 5.8: N-nitrosamines derived from areca nut alkaloids

1. Raw or green (undried)
2. Sun dried
3. Boiled

Raw and sun dried areca nuts have higher alkaloid and tannin content in comparison to boiled areca nuts. The areca nut chewers generally swallow the saliva completely, thus bathing the esophageal lining with the genotoxins released during chewing. The swallowing of saliva has been blamed for the increased rate of esophageal cancer. However, those who chew areca nut plus tobacco, expectorate the saliva periodically because of the bitter taste of tobacco. Currently the habit of areca nut chewing is recognized as the most important etiologic agent in oral submucous fibrosis or OSF.

ALCOHOL

The main component of alcoholic beverages is ethyl alcohol and water. According to Kabat and Wynder, the main carcinogenic agent in alcoholic beverages is ethyl alcohol or ethanol. In addition, present in the alcoholic beverages are many polycyclic aromatic hydrocarbons. The actions of alcohol are local and systemic. Ethyl alcohol is metabolized to acetaldehyde in the liver. In the next step, acetaldehyde is converted to acetic acid in the liver. These metabolic steps cause damage to the hepatocytes because of acetic acid and acetaldehyde. Thereby reducing the absorption of nutrients from the intestine, leading to nutritional deficiency and immunodeficiency.

Local Action

Ethyl alcohol dissolves the lipid layer of epithelial cells of the oral mucosa as a result it helps in the penetration of carcinogens. Thus mainly acting like a cocarcinogen. As a result, people who drink and smoke at the same time are more prone to developing oral cancer.

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Chapter

6

Oral Precancer

INTRODUCTION

Oral cancer makes up approximately 3 % of all malignancies of the body, although in some parts of the world, that percentage is much higher. The majority of oral cancers consist of oral squamous cell carcinoma. A number of such carcinomas develop from preexisting pathologies, so called precancerous lesions and precancerous conditions.

The most common oral precancerous lesion is a whitish change of the oral mucosa, an oral leukoplakia. The development of oral cancer may also be promoted by certain precancerous conditions such as oral submucous fibrosis, erosive lichen planus, syphilitic glossitis, sideropenic dysphagia (Paterson-Kelly syndrome, Plummer-Vinson syndrome), discoid lupus erythematosus, tylosis (palmoplantar hyperkeratosis), and dyskeratosis congenita.

PRECANCEROUS LESION

A precancerous lesion is defined as a morphologically altered tissue in which cancer is more likely to occur than in its apparently normal counter part. Leukoplakia and erythroplakia occurring separately or in combination are the most common precancerous oral lesions. Examples of precancerous lesions include:

1. Oral leukoplakia
2. Erythroplakia
3. Smokers palate
4. Actinic cheilitis

PRECANCEROUS CONDITION

A generalized state associated with a significantly increased risk of cancer. Examples of precancerous conditions include:

1. Oral submucous fibrosis
2. Erosive lichen planus
3. Syphilitic glossitis
4. Sideropenic dysphagia
5. Discoid lupus erythematosus
6. Dyskeratosis congentia
7. Tylosis

ORAL LEUKOPLAKIA

Sir James Paget had recognized the malignant potential of oral leukoplakia and its relationship to pipe smoking, reporting on leukokeratosis and smoker's patch as early as 1851. A quarter century before Schwimmer from Budapest coined the term leukoplakia in 1877. One hundred forty years later, oral leukoplakia is well established as one of the very best examples of premalignancy in man.

Leukoplakia is not only the most common oral precancerous lesion, representing 85 % of such

lesions, but also the most common of all chronic lesions of the oral mucosa. The rate of malignant transformation of oral leukoplakia ranges from 0.13 % to 6 %.

Definition

The first recorded white oral plaque was an icthyosis reported in 1818 by Alibert of Paris.

More than any other disease, oral leukoplakia has suffered from an excess of diagnostic terms and definitions; at least 75 have been used so far. This lead to such confusion that many clinicians refuse to use any term beyond white patch. Accordingly, whitish patches or plaques associated with use of tobacco should be listed as tobacco-associated oral leukoplakias.

The WHO in 1978 defined oral leukoplakia as "A white patch or plaque that cannot be characterized clinically or histopathologically, as any other disease." At the international seminar held in 1983, the previous definition was changed to: "Leukoplakia is a whitish patch or plaque that cannot be characterized clinically or pathologically as any other disease and it is not associated with any physical or chemical causative agent except for the use of tobacco." Whitish patches or plaques related to local causes other than tobacco usage should be listed according to the known cause and not be termed leukoplakias. Examples of such lesions are frictional lesions, lesions associated with dental restorations, lesions associated with cheek biting and glassblower's lesion.

In 1994, at another symposium on oral white lesions with special reference to precancerous and tobacco-related lesions the definition of oral leukoplakia was changed to: "Oral leukoplakia is a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion; some oral leukoplakias will transform into cancer." In that report, a distinction was made between a provisional clinical diagnosis of oral leukoplakia and a definitive one.

A provisional clinical diagnosis is made when a lesion at the initial clinical examination cannot be clearly diagnosed as any other disease of the oral mucosa with a white appearance; a definitive clinical diagnosis of oral leukoplakia is made as a result of the identification, and if possible elimination, of suspected etiological factors and, in the case of persistent lesions (no signs of regression within 2-4 weeks), histopathological examination.

Epidemiology

The prevalence of oral leukoplakia varies considerably when findings from various countries are compared. These geographic differences could probably be explained largely by differences in tobacco habits and by the use of different criteria. The onset of oral leukoplakia usually takes place after the age of 30 years, resulting in a peak incidence above the age of 50 years.

Oral leukoplakias seems to most prevalent among men, except for some areas in India, where certain tobacco habits are common among women. The most affected oral sites are the commisures, buccal mucosa (60-90 %). Next are the lip (3.7 %), the alveolar ridge (3.0 %), the tongue (1.4 %), the floor of the mouth (1.3%), the vestibular mucosa (1.1 %), and the palate (0.9%). Homogenous oral leukoplakias are much more prevalent than non-homogenous oral leukoplakias; while tobacco associated oral leukoplakias are more prevalent than idiopathic oral leukoplakias.

ETIOLOGY OF ORAL LEUKOPLAKIA

The etiology of oral leukoplakia remains unknown. Many physical agents have been proposed, including tobacco, alcohol,

microorganisms, ultraviolet radiation, and chronic friction.

Tobacco Smoking

Tobacco smoking is by far the most accepted. The evidence for a tobacco smoking etiology for oral leukoplakia, however, is quite strong. Not only do 70% to 90% of oral leukoplakia patients have such habit, but also 78% of lesions either completely disappear or regress within 12 months after smoking cessation. Ironically, oral leukoplakias remaining after habit cessation or in persons who have never smoked may have a higher risk of malignant transformation than oral leukoplakias in smokers.

Alcohol

Alcohol as an independent etiological factor in the development of oral leukoplakia is still questionable.

Microorganisms

Microorganisms have been implicated in the etiology of oral leukoplakia for more than a century, beginning with the classic dorsal leukoplakia of syphilitic glossitis. Today tertiary syphilis is rare, but *Candida albicans* is so often found in Phase III and Phase IV lesions that the terms candidal epithelial hyperplasia and candidal leukoplakia are commonly used to describe them. It is not known whether this yeast produces dysplasia or secondarily infects previously altered epithelium, but some oral leukoplakias have disappeared or have become altered to a homogenous oral leukoplakia after topical antifungal therapy.

In recent years, the possible role human papilloma virus type 16 in the pathogenesis of oral leukoplakia has also been discussed, particularly with regard to Phase III oral leukoplakia. However, human papilloma virus type 16, demonstrated in oral leukoplakias and carcinomas, has been shown to induce dysplasia in squamous epithelium in a sterile *in vitro* environment.

Ultraviolet Radiation

Ultraviolet radiation is also an accepted etiologic factor for oral leukoplakias, but only those associated with actinic cheilitis or "farmer's lip." Two-thirds of all lip vermilion carcinomas are associated with oral leukoplakia.

Chronic Friction

Chronic mechanical irritation is no longer considered important to the production of oral leukoplakia. Such obvious traumatic lesions as linea alba buccalis and chronic cheek bite have never been reported to transform into malignancies. White lesions produced by mechanical irritation are best considered frictional keratoses, which have no potential for malignant transformation.

CLINICAL FEATURES

Oral leukoplakia has a varied clinical appearance and its appearance changes over time (Table 6.1).

Phase I — Preleukoplakia (Fig. 6.1)

Oral leukoplakias begin as thin, gray or gray-white plaques that may appear somewhat translucent, are sometimes fissured or wrinkled, and are typically soft and flat. They usually have sharply demarcated borders but occasionally blend gradually into normal mucosa.

Phase II—Homogenous Leukoplakia (Fig. 6.2)

Phase I oral leukoplakias may disappear or continue unchanged, but as time progresses preleukoplakia may extend laterally and acquire a distinctly white appearance due to thickening keratin layer. They may exhibit shallow cracks

Table 6.1: Various diagnostic descriptive terms used for Phase I to Phase IV leukoplakia subtypes

Phase	Diagnostic Term	Risk of Malignant Transformation
I	Thin leukoplakia, Preleukoplakia, Homogeneous leukoplakia	+/–
II	Thick, smooth leukoplakia, Fissured leukoplakia, Homogenous leukoplakia	++
III	Granular leukoplakia, Verruciform leukoplakia, Rough leukoplakia, Candidal epithelial hyperplasia, Homogenous leukoplakia	+++
IV	Erythroleukoplakia, Speckled leukoplakia, Candida leukoplakia, Nonhomogenous leukoplakia	++++

Fig. 6.1: Preleukoplakia

Fig. 6.2: Homogenous leukoplakia

and have a smooth, wrinkled, or corrugated surface with a consistent leathery texture throughout and are referred to as homogenous oral leukoplakia. Homogenous oral leukoplakia remains indefinitely in this phase, but some regress or disappear and a few become even more severe.

Phase III—Verruciform Leukoplakia (Fig. 6.3)

Phase II oral leukoplakias begin to develop surface irregularities and are referred to as granular or nodular oral leukoplakia. Occasionally, pointed projections develop on the surface and the resulting lesions are called verruciform oral leukoplakia.

Phase IV—Speckled Leukoplakia (Fig. 6.4)

Phase III oral leukoplakias begin to develop multiple circular or oval patches of redness in scattered areas. Such areas presumably represent sites in which epithelial cells are so immature that they are no longer able to produce keratin. These intermixed red and white Phase IV lesions (*erythroleukoplakia, speckled leukoplakia, or nonhomogenous leukoplakia*), are the most worrisome form of the disease, and carry an extremely high risk of malignant transformation.

LSCP CLASSIFICATION AND STAGING SYSTEM (Table 6.2)

In order to promote uniform reporting of various aspects of oral leukoplakia, there is a need for a classification and staging system in which the site, the clinical subtype and the histopathological features are taken into account. The staging system (Stages I-IV) has not yet been proven to be of value with regard to the management of the patient. A somewhat debatable item that has been included in the

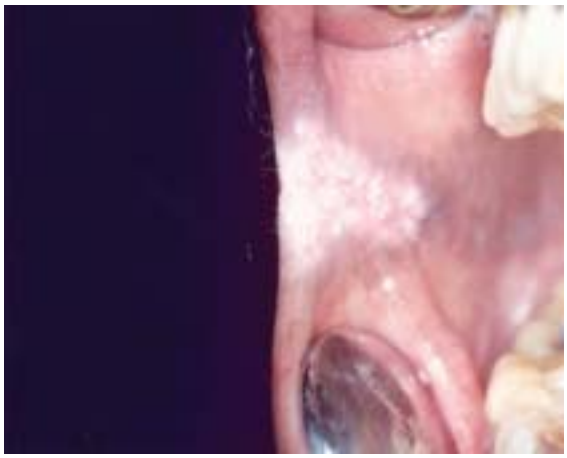

Fig. 6.3: Verruciform leukoplakia

Fig. 6.4: Speckled leukoplakia

Table 6.2: LSCP-classification and staging system for oral leukoplakia

1st symbol (L) represents the size

L_0 = No evidence of lesion

L_1 = lesion $\leq$ 2 cm

L_2 = Lesion 2-4 cm

L_3 = Lesion > 4 cm

L_X = Not specified

2nd symbol (S) represents the site

S_1 = All oral sites, except for the floor of the mouth and tongue

S_2 = Floor of the mouth and tongue

S_X = Not specified

3rd symbol (C) represents the clinical aspect

C_1 = Homogenous

C_2 = Nonhomogenous

C_X = Not specified

4th symbol (P) represents the histopathological features

P_1 = No dysplasia

P_2 = Mild dysplasia

P_3 = Moderate dysplasia

P_4 = Severe dysplasia

P_X = Not specified

Staging is only preformed in leukoplakias that have been examined histopathologically

Stage I = Any L, S_1, C_1, P_1, or P_2

Stage II = Any L, S_1, C_2, P_1, or P_2; any L, S_2, C_1, P_1, or P_2

Stage III = Any L, S_2, C_2, P_1, or P_2

Stage IV = Any L, any S, any C, P_3, or P_4

staging system is the assumption that there are, high-risk sites (tongue and floor of the mouth), which may be true in certain parts of the world, e.g., North America and Europe, but not so in other parts, e.g., India.

Differential Diagnosis

Differential diagnostic problems may arise clinically with candidosis, oral lichen planus, discoid lupus erythematosus, and white sponge nevus. The commonly used term "Candida-associated oral leukoplakia" leaves the question unsettled, whether one is dealing with oral leukoplakia or with another disease entity, in particular candidosis. It is suggested, that those "Candida-associated oral leukoplakias" which, after antimycotic treatment and cessation of smoking, disappear completely, should be termed as candidosis. In case of a residual lesion, the term oral leukoplakia should be maintained.

Investigations

Although the experienced may be able to diagnose and manage the majority of oral leukoplakias on clinical grounds only in general, such practice should be discouraged, even in asymptomatic, homogenous leukoplakias. This holds true while dealing with leukoplakic lesions in high risk sites such as the ventral aspect of the tongue and the floor of the mouth. Exfoliative cytology and application of toluidine blue are of limited value in the diagnosis of oral leukoplakia.

The most reliable information is provided by histopathological examination of biopsy. In lesions less than 1 cm in diameter, an excisional biopsy can be carried out, while in lesions greater than 1 cm in diameter, an incisional biopsy should be taken which should be taken, which should include the most suspicious area as judged from clinical evaluation. In multiple oral leukoplakias, one may consider of taking multiple biopsies.

Histopathology

In order to arrive at a definitive diagnosis of oral leukoplakia it is mandatory that a biopsy should be taken and that a histopathological report is available. If an oral precancerous lesion is suspected clinically, the histopathological report should always include a statement on the presence or absence of epithelial dysplasia and, if present, an assessment of its severity.

Individual cellular changes should be refered to as "atypia" and the general disturbance in the epithelium as "dysplasia." Regressive alterations in the cells such as alteration in their size, shape, orientation, and functions are termed as dysplasia.

Oral leukoplakias, which show epithelial dysplasia, carry an increased risk of malignancy. Dysplasia may be graded as mild, moderate, severe and carcinoma in situ.

1. Mild: The dysplastic features are towards lower third of the epithelium
2. Moderate: The dysplastic features occupy two thirds
3. Severe: The dysplastic features occupy more than two thirds of the epithelial thickness, but less than full
4. **Carcinoma *in situ*** (intraepithelial carcinoma)**:** All the features of dysplasia are present but the basement membrane is intact and there is no invasion

The World Health Organization collaborating reference centre for oral precancerous lesions (1978) mentions the following changes as possibly occurring in epithelial dysplasia (Table 6.3)

1. **Drop-shaped rete pegs:** The drop-shaped rete pegs are wider at their deeper aspect than the superficial aspect.
2. **Disturbed nuclear polarity:** The nuclei in the basal cell layer are irregularly disposed in comparison to the nuclei in the basal cell layer of normal stratified squamous epithelium where they are more or less in the same position.

Table 6.3: Dysplastic features
Drop-shaped rete pegs
Disturbed nuclear polarity
Basal cell hyperplasia
Disturbed epithelial cell maturation
Pleomorphic cells and nuclei and anisocytosis
Hyperchromatic nuclei
Prominent nucleoli
Increased nucleocytoplasmic ratio
Cell crowding
Increased mitosis, superficial mitosis and abnormal mitosis
Reduced cellular cohesion
Keratinization below surface

3. **Disturbed epithelial maturation:** Disturbed maturation of the epithelial cells may extend for varying distances throughout the stratified squamous epithelium and may even occur to its entire thickness.
4. **Basal cell hyperplasia:** Because of disturbed epithelial maturation, the basal cells do not mature into typical polyhedral keratinocytes. Thus, the cells retain the morphology of the basal cells.
5. **Pleomorphic cells, nuclei, and anisocytosis:** There are cells and nuclei, which are of different shapes, and sizes instead of demonstrating the regularity in found in normally maturing stratified squamous epithelium.
6. **Hyperchromatic nuclei:** The nuclei are more basophilic than the normal keratinocytes.
7. **Prominent nucleoli:** The nucleoli are prominent and may be seen singly or in multiples in different nuclei.
8. **Increased nucleocytoplasmic ratio:** Increased nucleocytoplasmic ratio observed in dysplasia is due to decrease in cytoplasmic volume and increase in the size of the nucleus which may fill or almost fill an entire keratinocyte.
9. **Cell crowding:** Due to disturbed cellular maturation, there is more number of cells in a given area.
10. Increased mitosis, superficial mitosis and abnormal mitosis may be found to different extents in epithelial dysplasia.
11. **Reduced cellular cohesion:** Reduced cellular cohesion is because their attachments are reduced or faulty.
12. **Keratinization below surface:** Keratinization within the cytoplasm of individual cells is known as intraepithelial keratinization or it may occur in relation to a small cluster of cells.

TREATMENT

Management of oral leukoplakia includes removing all etiological factors to determine the possibility of reversibility. The time required for oral leukoplakia to regress after elimination of suspected etiological factors may vary from several weeks to months. When there are no signs of regression within 2-4 weeks after attempted elimination of etiological factors, surgical excision is the only established method of controlling oral leukoplakia.

Treatment with carbon dioxide laser has been the most valuable approach based on the biological effects of laser on oral tissues, ease of operation, low incidence, and good control. The key is long-term follow-up after removal, because recurrences are frequent and additional oral leukoplakias occur. Clinical evaluation every 6 months is recommended; evaluation every 2 to 3 months is necessary for Phase IV lesions. Treatment sites remaining disease free for 3 years need no follow-up.

Alternative approaches to control oral leukoplakia include vitamin A, retinoic acid, and β-carotene, which is the precursor of vitamin A. Vitamin A, is not reproducibly effective, although

by mechanisms not understood, it will induce dekeratinization in some lesions. The role of antioxidant supplements is less certain and their use less predictive.

Prognosis

Lesions of long duration have a greater risk of malignant transformation than those of short duration, and the older the oral leukoplakia, the worst is its prognosis. The risk of malignant transformation of oral leukoplakia is more common in women than in men. Homogenous oral leukoplakias carry lower risk of malignant transformation, while nonhomogenous oral leukoplakias carry a higher risk and the location of the lesion is important, since apparently similar lesions in different oral sites may carry different risks of malignant change. For example, leukoplakia affecting the floor of the mouth or the ventral surface of the tongue appears to carry a high risk. In general, it is assumed that approximately 5 % of all oral leukoplakias with an initially noncarcinomatous histologic picture will transform into malignancy in an average period of five years.

ERYTHROPLAKIA

Historical Aspect

In 1911, Queyrat described a sharply defined, bright red, glistening velvety precancerous lesion of the glans penis, which was termed "erythroplasie." Queyrat used the term "erythroplasie" to designate a red area (plaque) by analogy to the French term "leucoplasie." Shear clearly pointed out that if the English word leukoplakia is matched with "leucoplasie", then Queyrat's "erythroplasie" should be translated into English "erythroplakia." When exactly the term "erythroplakia" was introduced to describe a specific type of oral mucosal lesion is not well documented.

Definition

The term erythroplakia (erythroplasia) was coined to describe red lesions of the oral mucosa in contrast to oral leukoplakia. Over the years, several definitions of oral erythroplakia have been suggested. The WHO in 1978 defined oral erythroplakia as "lesions of the oral mucosa that present as bright red patches or plaques that cannot be characterized clinically or pathologically as any other condition." This definition was confirmed during an International seminar on oral leukoplakias and associated lesions related to tobacco habits in 1983.

In 1994, at another symposium on oral white lesions with special reference to precancerous and tobacco-related lesions the definition of oral erythroplakia was changed: "The term erythroplakia is used analogously to leukoplakia to designate lesions of the oral mucosa that present as red areas and cannot be diagnosed as any other definable lesion." The same comments apply in relation to provisional and definitive diagnosis as for oral leukoplakias. In the second edition of 'Histological typing of cancer and precancer of the oral mucosa' erythroplakia was defined as "A fiery red patch that cannot be characterized clinically or pathologically as any other definable lesion." This definition is now widely accepted, although it is based on the principle of diagnosis per exclusion.

Prevalence

It is generally accepted that oral erythroplakia is less common than oral leukoplakia. Oral erythroplakia has range of prevalence between 0.02% and 0.83%.

Clinical Features

Age: Oral erythroplakia mainly occurs in the middle aged and the elderly.

Gender: Recently it has been stated that oral erythroplakia occurs mostly in men. With the few

studies available indicating gender distribution this statement cannot be sustained.

Location and size: The soft palate, the floor of the mouth, and the buccal mucosa are most commonly affected by oral erythroplakia. The typical lesion is less than 1.5 cm in diameter.

ETIOLOGY

Etiology and pathogenesis of oral erythroplakia are poorly understood. Predisposing factors are widely unknown, but it was suggested that tobacco and alcohol use are probably involved in most cases.

Clinical Appearance

The WHO Histological typing of cancer and precancer of the oral mucosa described the clinical features of oral erythroplakia as follows: "Some erythroplakias are smooth and some are granular or nodular. Often there is a well-defined margin adjacent to mucosa of normal appearance."

Shear elaborated on the different clinical variants of oral erythroplakia: "Although erythroplakic lesions may have a smooth velvety surface, they may also be seen with other morphological characteristics. They may have an irregular, red granular surface interspersed with white or yellow foci, which may be described as granular erythroplakia. There may be numerous, small irregular foci of leukoplakia dispersed in the erythroplakic patch, and this has been called speckled leukoplakia.

Oral erythroplakia is soft to palpation and does not become indurated or hard until carcinoma develops in it. Oral erythroplakia, while occasionally associated with oral leukoplakias and oral squamous cell carcinoma, may also be observed in association with other mucosal diseases, in particular oral lichen planus.

Histopathology

Histopathologically, oral erythroplakia tends to show dysplasia, often in a distinctive pattern with drop-shaped rete processes, marked nuclear and cellular pleomorphism and minimal keratinisation. Oral erythroplakia is typically diagnosed microscopically as severe epithelial dysplasia or carcinoma *in situ*.

Rate of Malignant Transformation

Oral erythroplakia has a high risk of malignant transformation compared to all other oral mucosal lesions (oral leukoplakia, erosive lichen planus, and oral submucous fibrosis). The high risk of malignant transformation is because histopathologically oral erythroplakia typically presents as severe epithelial dysplasia or carcinoma *in situ*. Generally, the rate of malignant transformation in oral precancerous lesions diagnosed histopathologically as severe epithelial dysplasia or carcinoma *in situ* varies from 14 % to 50 %.

Differential Diagnosis

From the clinical point, diseases of the oral mucosa with red (erythematous) changes should be considered as differential diagnosis. Of the diseases with red (erythematous) changes, atrophic candidosis, and erosive lichen planus are the most important. Biopsy is mandatory in cases of doubt.

Treatment

Oral erythroplakia has a high risk of malignant transformation and therefore early effective treatment is compulsory. The recommended treatment has been surgical excision of lesions with severe epithelial dysplasia or carcinoma *in situ* with regular follow-up.

Oral Submucous Fibrosis

In 1952, Schwartz described a fibrosing condition in the mouths of 5 Indian women from Kenya, for which he called "atrophia idiopathica tropica mucosae oris." Later it was termed oral submucous fibrosis (OSF). OSF is an insidious, chronic disease affecting any part of the oral cavity and sometimes the pharynx.

OSF is a precancerous condition with a high risk of malignant transformation (7.6%). The estimated prevalence of OSF is 0.2 to 0.5% in the general Indian population. Unlike oral leukoplakia, OSF is not known to regress when the person stops chewing areca nut. The condition may remain unchanged or become severe.

Synonyms

Diffuse oral submucous fibrosis
Idiopathic scleroderma of the mouth
Idiopathic palatal fibrosis
Sclerosing stomatitis
Juxta-epithelial fibrosis

Geographic Distribution

There is no relationship between oral submucous fibrosis and any community or religious group. Oral submucous fibrosis predominantly occurs among Indians or Indians settled in other countries. It occasionally occurs in other Asiatics and sporadically among non-Asians.

Etiology and Pathogenesis

The etiology of OSF is multifactorial and the patients are genetically predisposed, which makes their oral mucosa susceptible to chronic inflammatory changes if they chew areca nut.

Chilies

The use of chilies was suggested as possible etiologic factor as patients with OSF were unable to tolerate spicy food and that the disease was due to some form of hypersensitivity to capsaicin, an irritant, which is present in chilies.

Systemic Factors

It was also suggested that OSF was a mucosal change secondary to chronic iron and / or vitamin B-complex deficiency and is an Asian analogue of Plummer-Vinson syndrome.

Autoimmunity

An autoimmune response to an antigenic stimulus may manifest as chronic inflammation, which comes before the fibrotic changes in the oral mucosa. Human leukocyte antigens (HLA) are a series of proteins and their genes are located at a number of loci along the short arm of chromosome 6. The main loci are designated A, B, C, DR (D-related). HLA antigens are detectable on the surface of most nucleated cells e.g., basal cell layer of the epithelium. HLA-DR positive cells in the basal cell layer of the epithelium may act as antigens, resulting in infiltration of HLA-DR positive CD4 lymphocytes in the lamina propria. Thus, the presence of HLA-DR positive cells, Langerhans cells, and HLA-DR positive CD4 lymphocytes in OSF tissues suggests that there is a persistent antigenic challenge within the epithelium resulting in cellular immune response. It is likely that this chronic inflammation would enhance the permeability of the epithelium to areca nut alkaloids, flavanoids, and tannins, which could then alter the synthesis and breakdown of the subepithelial collagen.

Areca Nut

However, currently the habit of areca nut chewing is recognized as the most important etiologic agent. The fact that OSF is a permanent condition, which does not resolve after the cessation of the areca nut habit, indicates a permanent cellular change in the affected mucosa. As the amount of collagen in any tissue

is a result of the equilibrium between synthesis and degradation, an increase in resistance to collagenase would favor accumulation. The areca nut alkaloids stimulate the fibroblasts to produce collagen, inhibit the fibroblasts to produce collagenase, inhibit the fibroblast phagocytosis, and may stimulate the fibroblasts to produce lysyl oxidase, which converts soluble monomers of collagen and elastin into insoluble fibers. The tannins of areca nut may stabilize the collagen by forming cross-links between the peptide chains rendering the cleavage sites inaccessible to collagenase.

The bulk of connective tissue consists of cross-linked insoluble Type 1 collagen. Collagen synthesis is due to excessive production by fibroblasts and not due to excessive proliferation of fibroblasts. Hydroxy proline is an amino acid found only in collagen, and is incorporated in the collagen as 4-hydroxy proline. This reaction requires iron and ascorbic acid. The decreased plasma ascorbate and iron concentrations may be due to their utilization in the fibrosis process. It is well-established that fibroblasts and proliferating basal cells of the epithelium produce collagenase and that fibroblasts ingest segments of collagen after its breakdown by collagenase. A characteristic feature of OSF is atrophy of epithelium, which would decrease the production of collagenase by the basal cells and enhance the penetration of the tannins. Therefore, a more likely explanation for decreased collagen breakdown would be due to interference with either collagenase production or collagen degradation by cells or both.

Clinical Presentation

Patients may describe a sudden attack of burning sensation in the mouth while consuming spicy food, appearance of vesicles especially on the palate, ulcerations of the oral mucosa, excessive salivation, altered taste sensation, and xerostomia (Table 6.4). The major presenting complaint is inability to open the mouth due to

Table 6.4: Signs and symptoms of oral ulcer

Oral Symptoms	Oral Signs
Dryness of mouth	Fibrous bands
Burning sensation	Sensitivity to palpation
Altered taste	Limitation of mouth opening
Referred pain in the throat/ear region	Blanching of oral mucosa
Numbness in the mouth	Atrophy of the tongue
Vesicles and ulcers	
Dysphagia	

accumulation of inelastic fibrous tissue in the oral mucosa (Fig. 6.5). The buccal mucosa and lips may be affected at an early stage. In the buccal mucosa, a mottled, marble-like appearance may be seen where the dense, pale, blanched, fibrosed areas alternate with pinker, more normal oral mucosa (Fig. 6.6). The blanching occurs due to impairment of local vascularity. The oral mucosa is involved symmetrically and the fibrous bands in the buccal mucosa run in a vertical direction. The fibrosis progresses into the posterior part of the buccal mucosa, the anterior pillar of the fauces and the soft palate. The fibrous tissue is seen arching from the anterior pillars of the fauces into the soft palate as a delicate reticulum of interlacing white strands, which later become

Fig. 6.5: Inability to open the mouth

merged (Fig. 6.7). The uvula becomes small and distorted. If the fibrosis extends into the esophagus, the patient may experience dysphagia, and reduced esophageal mobility. The fibrosis leads to difficulty in opening the mouth, difficulty in mastication, speech, swallowing, blowing, whistling, and referred pain in the throat, and ears.

As the disease progresses the floor of the mouth becomes pale and thickened, there is atrophy of the tongue papillae (Fig. 6.8), impairment of tongue movements (Fig. 6.9) and reduction in size of the tongue. Fibrous circular palpable bands develop around the entire rima oris. In advanced stages, the jaw may be inseparable, and the inelastic mucosa is forced against the buccal aspects of the teeth where sharp edges or restorations may cause ulceration, which becomes secondarily infected. At any stage in the disease, the epithelium may become the site of nonspecific ulceration, dysplastic change, or malignant transformation.

Fig. 6.6: Blanching of buccal mucosa

Fig. 6.7: Impairement of tongue movements

Fig. 6.8: Atrophy of tongue

Fig. 6.9: Impairement of tongue movements

Clinical Grading

Depending upon the clinical condition, OSF is graded for the purpose of treatment as :

Grade I—Only blanching of oral mucosa without symptoms

Grade II—Burning sensation, dryness of mouth, vesicles or ulcers in the mouth

Grade III—In addition to grade II, restriction of mouth opening
Grade IV—In addition to grade III, palpable fibrous bands all over the mouth
Grade V—Grade IV and tongue is involved
Grade VI—OSF with histopathologically proven oral cancer

HISTOPATHOLOGY

Connective Tissue

The connective tissue changes are always associated with chronic inflammatory reaction beneath the basement membrane (juxta-epithelial). The chronic inflammatory cell infiltrate consists of lymphocytes, plasma cells, monocytes, and macrophages. Disruption of the basal cell layer of the epithelium by chronic inflammatory cells is seen. The chronic inflammatory reaction is followed by accumulation of collagen beneath the basement membrane, which undergoes fibroelastic transformation or hyalinization.

Connective tissue exhibits thick, dense bundles of collagen fibers. Because of fibrosis of connective tissue, the blood vessels become narrow. The narrowing of the blood vessels appears first in the upper connective tissue and spreads gradually downwards. A relative reduction in vascularity leads to atrophy of the overlying epithelium. The bundles of collagen fibers may extend downwards and involve the underlying striated musculature, which may later undergo degeneration.

Epithelium

The epithelial changes are usually secondary to the connective tissue changes especially due to connective tissue fibrosis resulting in narrowing of blood vessels. Histopathologically, OSF is associated with marked atrophy of the oral epithelium (epithelium is thin) with loss of rete-ridges. Epithelial atrophy is marked in advanced stages of the disease. The atrophic epithelium is one of the cardinal light microscopic features of OSF and is more vulnerable to carcinogens, which in India are so often present in the form of tobacco. This atrophy of the oral epithelium may be of severe degree at focal sites resulting in ulcerations with exposure of the underlying connective tissue. The atrophic epithelium first becomes hyperkeratotic (clinically leukoplakic), and later intercellular edema and basal cell hyperplasia develop, eventually followed by epithelial atypia with moderate epithelial hyperplasia. From then on carcinoma may develop any time.

TREATMENT MODALITIES

Conservative

1. Stoppage of the habit
2. Biopsy to confirm the diagnosis and to reveal any dysplasia
3. Treatment of any periapical and periodontal disease which may have aggravated or caused restricted mouth opening
4. Nutritional therapy (vitamin B-complex and iron supplements, antioxidants)
5. Topical application of anesthetics and corticosteroids
6. Physiotherapy by the means of microwave diathermy using microtone 200 unit producing microwaves to relieve trismus. One sitting of 20 minutes a day for 15 days.
7. Inj hyaluronidase 1500 IU 0.5 ml injected intralesionally twice a week for 10 weeks (hyaluronidase breaks down hyaluronic acid, lowers the viscosity of the intercellular cement substances and decreases collagen formation).
8. Inj dexamethasoe 1.5 ml with 0.5 ml lignocaine hydrochloride injected intralesionally twice a week for 5 weeks (corticosteroids act as immunosuppressive

agents and anti-inflammatory agents, thereby preventing fibrosis by decreasing fibroblasts proliferation and deposition of collagen).

9. Inj placental extracts (aqueous solution of human placenta) 2 ml intralesional once a week for 4 weeks, the mode of action of placentrex is thought to be by biogenic stimulation (i.e., by accelerating cellular metabolism through the pituitary-adrenal cortical axis, assisting in the absorption of exudate, stimulating the regeneration process, increasing the physiological actions of organs, anti-inflammatory and analgesic effect, and increase in blood circulation and tissue vascularity). The placentrex is rich in steroids, proteins, chorionic gonadotrophins, estrogens, and progesterones.

Surgical

Surgical treatment is the method of choice in patients with marked limitation of mouth opening and in cases where the biopsy has revealed dysplastic or neoplastic changes. Enlisted below are some of the effective surgical methods:

1. Split-thickness skin-grafting following bilateral temporalis myotomy or cornoidectomy.
2. Submucosal resection of fibrotic bands and replacement with a partial thickness skin or mucosal graft.
3. Surgical excision of the fibrotic bands with submucosal placement of fresh human placental grafts, followed by local injections of dexamethasone.
4. Resection of the fibrotic bands with lasers.

Following surgery the mouth is maintained open with a pair of small, smooth rubber anesthesia props to produce an interincisal opening of 35-40 mm. The patient is fed by means of a fine-bore nasogastric tube for 7 days. Daily mouth opening exercises and nocturnal props are required for a further 4 weeks.

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Chapter 7

Oral Cancer

INTRODUCTION

The word cancer was coined by Hippocrates. In Latin, cancer means "*Cancrum*" denoting Crab, thus reflecting the true nature of cancer since it adheres to any part that it seizes upon in an obstinate manner like the crab (Fig. 7.1). The term oral cancer is used to describe any malignancy that arises from the oral tissues. Squamous cell carcinoma is the most common, representing 90-95% of all oral malignancies. The term oral cancer is therefore used to imply squamous cell carcinoma.

It is one of the 10 most common cancers across the globe. Generally, oral cancers are more common among men than in women depending upon the type of tobacco habits prevalent among them. Oral cancer commonly occurs in the 6th decade of life.

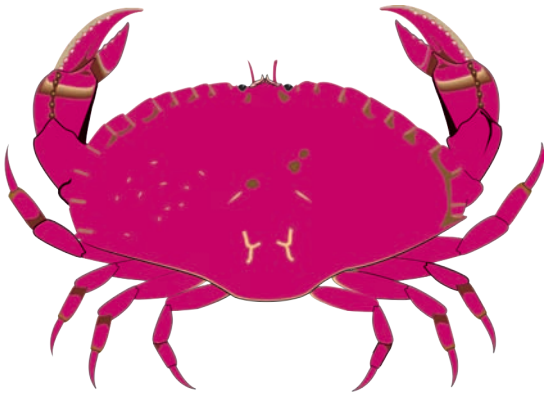

Fig. 7.1: Crab

GENETICS OF CANCER

Chromosomes

Each cell has a control center called a nucleus. The nucleus contains information, which tells the cell what to do and when to grow and divide. This information is contained in the chromosomes. In the nucleus of each human somatic cell (with the exception of sperm and egg cells), there are 23 pairs of chromosomes, for a total of 46 (22 pairs of autosomes and one pair of sex chromosomes). Therefore, human somatic cells are termed as diploid cells. However, the gametes are haploid and have a total of 23 chromosomes. Chromosomes are passed from parents to their children. One chromosome from each pair is inherited from the mother, and the other comes from the father. One of the chromosome pairs consists of sex chromosomes. In normal males, the sex chromosomes are a Y chromosome inherited from the father and an X chromosome inherited from the mother. Two X chromosomes are found in normal females, one inherited from each parent. This is why children resemble their parents, both physically and in their tendency to develop certain diseases.

Chromosomes are made up of long strands of DNA (deoxyribonucleic acid). Within each chromosome, there are about 30,000 to 40,000 genes. Genes are segments of DNA that tell the cell make a protein. The normal gene consists of three exons and two introns. For example, certain proteins help the cell divide into two cells, while others prevent the cell from dividing too often. A cell uses its genes selectively, that is, it will activate or "turn on" the gene it needs at the right moment. Some genes stay active all the time to produce proteins needed for basic cell functions. Genes, serve two roles in cancer: some contribute to the development of cancer and others protect individuals from cancer.

Mutations

Carcinogens transform normal cells by causing changes in the cell's DNA. These changes are called mutations, and the carcinogen is thus said to be mutagenic. A mutated gene may tell the cell to make an abnormal protein, which no longer functions normally. The mutated gene may not have any effect, or it may lead to a disease, e.g., cancer. Mutations can be either hereditary or acquired. Hereditary mutations are gene changes (mutations) that come from a parent and therefore exist in all cells of the body, including sperm and egg cells.

The mutation can be passed from generation to generation and are called germline mutations, e.g., sickle cell anemia. Hereditary mutations cause a small percentage of cancers. An acquired mutation occurs when DNA in a cell changes during the person's life. This can be caused by exposure to radiation, chemicals, and biological agents. Acquired mutations do not exist in all cells of the body, including sperm and egg cells and therefore cannot be passed from generation to generation.

It is important to realize that mutations occur at all the time in our cells and are repaired. If the mutation cannot be repaired, the cell begins a process called apoptosis that leads to its death. If the mutation occurs in a gene that controls cell division, it may lead to cancer or cancer may occur if the mutation happens in a gene that causes apoptosis. Cancer may also develop in people who inherit genes that make them prone to cancer along with acquired mutations. Therefore, some people may be more likely to develop cancer than others simply due to their genes. Mutations that have been found are point mutation, gene amplifications, gene deletions, and chromosomal translocations (Table 7.1).

Table 7.1: Genetic changes that convert protooncogenes into oncogenes

Type of change	Description and examples
Point mutation	Point mutations results due to the substitution of one nucleotide for another, resulting in a change in the amino acid sequence. Point mutations of Ras protein (glycine is replaced by valine) can convert Ras genes into Ras oncogenes.
Gene amplification	An abnormal increase in the copies of proto-oncogenes due to overreplication, resulting in an increased amount of gene product, thereby including cell profileration. *ErbB g*enes have been amplified in squamous cell carcinomas.
Gene deletion	Deletions of part of the coding region (exons) of a proto-oncogene can convert them into oncogenes. The *myc* oncogene can arise from its *myc* proto-oncogene by deletion.
Chromosomal translocation	A piece of chromosome may be translocated to another chromosome and affect the expression of genes at the breakpoint site. In Burkitt's lymphoma, a region of chromosome 8 is translocated to either chromosome 2, 14, or 22. The breakpoint in chromosome 8 causes the over expression of the *myc* gene.

The two main classes of genes that are now recognized to play a role in cancer are oncogenes and tumor suppressor genes.

Oncogenes

Oncogenes are mutated forms of genes that cause normal cells to grow out of control and become cancer cells. Oncogenes are a result of mutations of certain normal genes of the cell called proto-oncogenes. Proto-oncogenes are the genes that normally control how often a cell divides and to the degree, it differentiates. When a proto-oncogene mutates (changes) into oncogene, it becomes permanently activated or "turned on" and the cell divides quickly, which can lead to cancer (Figs 7.2A and B).

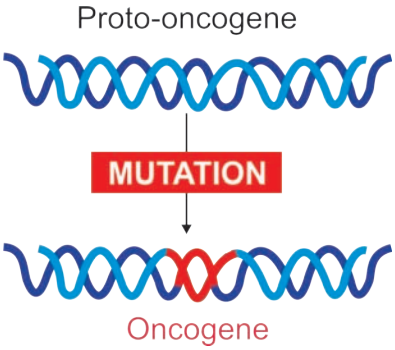

Fig. 7.2A: Proto-oncogene to oncogene

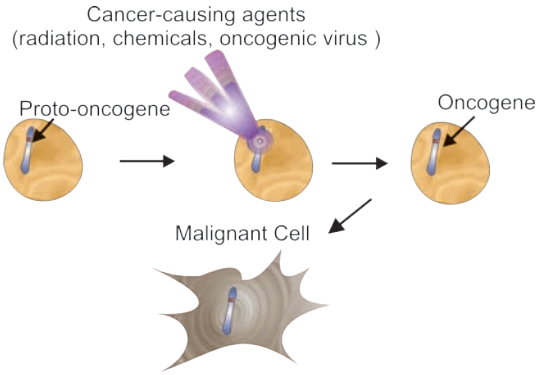

Fig. 7.2B: Proto-oncogene to oncogene

It may be helpful to think a cell as a car. The speed of the car is controlled by the brake. A proto-oncogene normally functions in a way that is similar to the brake. An oncogene could be compared to a brake that has failed, which causes the cell to divide out of control. In the somatic cells of the body, the cell cycle (Fig. 7.3) is regulated by different proteins. Scientists have divided these proteins into four different classes:

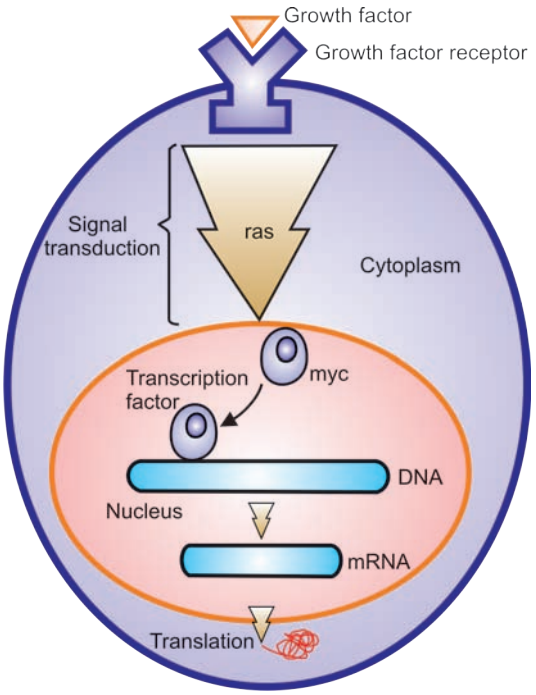

Fig. 7.3: Cell cycle regulation

1. **Growth factors:** The growth factors bind to the cell surface growth factor receptors and stimulate them. The best known of these is called *sis* gene, which encodes platelet-derived growth factor.
2. **Growth factor receptors:** The growth factor receptors are present on the cell membrane. These are normally turned "on" or "off" by growth factors. The best known of these is called *erbB* gene, which encodes epidermal

growth factor receptor. When the growth factor receptors are turned "on," they stimulate the cell to grow. In cancer, they are in a permanent "on" position (Fig. 7.4).

3. **Signal transducers:** These proteins are the intermediate pathways between the growth factor receptors and the cell nucleus where the signal is received. Like growth factor receptors, these can be turned "on" or "off." The best known of these is called *ras* gene, which encodes RAS protein. When a normal cell is stimulated through a growth factor receptor, inactive (GDP-bound) RAS is activated to a GTP-bound state. Activated RAS recruits RAF-1 and stimulates the (mitogen-activated protein) MAP-kinase pathway to transmit growth-promoting signals to the nucleus. However, an excited signal-transmitting state of RAS protein returns to a quiescent state because intrinsic guanosine triphosphatase (GTPase) hydrolysis GTP (guanosine triphosphate) to GDP (guanosine diphosphate). A family of GTPase-activating proteins (GAPs) acts as molecular brakes that prevent uncontrolled action of activated RAS protein by favoring hydrolysis of GTP to GDP. In cancer, the mutant RAS protein can bind to GAPs, but their GTPase activity fails to be increased. Thus the mutant RAS protein is trapped in its activated form, which leads to continuous stimulation of cells without any external trigger (Fig. 7.5).
4. **Transcription factors:** These final proteins tell the cell to divide. They act on the DNA. The best known of these is called *myc* gene, which encodes transcription factor. In cancer, they are in a permanent "on" position.

The oncogenes encode similar proteins that regulate the cell cycle. These include growth factors, growth factor receptors, signal transducers, transcription factors.

Tumor Suppressor Genes

Tumor suppressor genes are normal genes that activate genes that promote DNA repair, activate genes that arrest cell division, and activate genes that promote apoptosis. An important difference between oncogenes and tumor suppressor genes

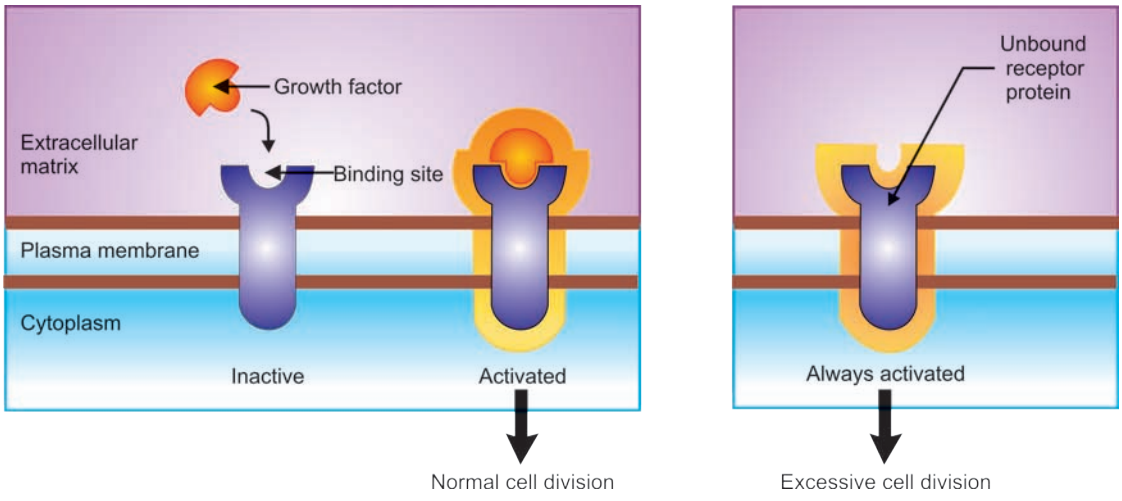

Fig. 7.4: Growth factors and cancer

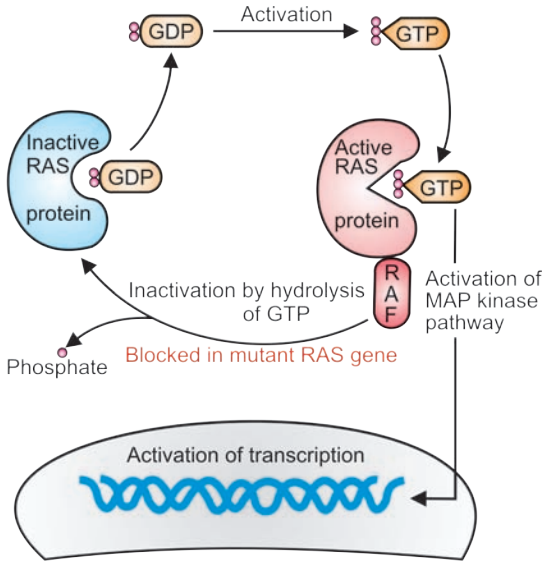

Fig. 7.5: Action of RAS protein

is that oncogenes develop from the activation (turning "on") of proto-oncogene, whereas tumor suppressor genes cause cancer when they are turned "off." Another major difference is that while the oncogenes develop from mutations during the life of the individual (acquired mutations), whereas tumor suppressor genes can be inherited as well as acquired. The *p53* tumor suppressor gene plays a central role in all three processes described below. Abnormalities of *p53* tumor suppressor gene can lead to head and neck cancers.

Types of Tumor Suppressor Genes

1. **DNA repair genes:** Every time a cell divides, it must duplicate its DNA. This process is not perfect, and copying errors occur sometimes. The copying errors are repaired by *p53* tumor suppressor gene. In cancer, the *p53* tumor suppressor gene is "turned off."
2. **Genes that arrest cell division:** The *p53* tumor suppressor gene arrests the cell division. In cancer, the *p53* tumor suppressor gene is "turned off" and the cells continue to grow, and can eventually become cancerous.
3. **Genes that promote apoptosis**: If there is too much damage to a cell's DNA, which cannot be fixed by DNA repair genes, the *p53* tumor suppressor gene destroys the cell by apoptosis or programmed cell death. If the *p53* gene is "turned off," cells with DNA damage continue to grow, and can eventually become cancerous.

ETIOLOGY

Although oral cancer has a multifactorial etiology, tobacco use and alcohol consumption are widely considered its major risk factors. According to WHO, about 90% of oral cancer in South-east Asia is attributable to tobacco use.

Carcinogens

Cancers can be induced in normal tissue by exposure to one of the three classes of carcinogenic agents: chemicals, radiation and oncogenic viruses. Of the three, it appears that long-term exposure to chemical carcinogens is responsible for most of the neoplasms arising in humans. It appears in particular that oral mucosal carcinomas are caused predominantly by chemical carcinogens, although there is evidence implicating viral and physical stimuli in the genesis of some oral neoplasms.

Chemical Carcinogens

Chemical carcinogens can be grouped into two categories. Some are direct-acting and require no chemical transformation to induce carcinogenicity (e.g., alkylating agents). However, the most are indirectacting carcinogens or procarcinogens, which require chemical transformation to induce carcinogeni-city (e.g., betel nuts). Most indirect-acting chemical carcinogens are activated chiefly by the cytochrome P-

450 dependent enzymes (monooxygenases) located in the endoplasmic reticulum or in the nucleus.

Chemical Carcinogenesis

Chemical carcinogenesis is a multi-step process involving two stages: initiation, and promotion. Experimental results has led to the assumption that oral cavity is more resistant to the effects of carcinogens than skin. This has been attributed to protective effects of saliva and the lack of structures in the oral mucosa such as hair follicles, and sebaceous glands, which might provide "portals of entry" in skin.

Initiation

All direct-acting and indirect-acting chemical carcinogens are highly reactive electrophiles (i.e., have electron deficient atoms) that react with electron rich atoms in DNA producing a chemical-DNA adducts. If the chemical-DNA adducts are not repaired by DNA repair genes, cell division takes place and the damaged DNA is transferred to the next generation of cells, each of which carries the mutation (damaged DNA).Although any gene may be the target of chemical carcinogens, *ras* gene and *p53* gene mutations are particularly common in several chemically induced cancers. Initiation is the first stage in carcinogenesis induced by chemical carcinogens.

Promotion

Promotion is the next stage in chemical carcinogenesis. Promotion differs from initiation in that there is no DNA damage and that the promoting agents increase the ability of an initiated cell to proliferate. The genetically damaged cell proliferates; giving rise to a clone of cells, each of which carries the same damaged DNA. As the clones of cells divide rapidly additional mutations occur, this further enhances those cells to proliferate. This process is known as clonal expansion. With progression the tumor mass becomes enriched with tumor cell variants (heterogeneity) i.e., they are nonantigenic, invasive, metastatic, and require fewer growth factors and are likely to be more aggressive.

Radiation

The portion of the electromagnetic spectrum is subdivided into ionizing radiation (X-rays, gamma rays, and cosmic rays) and non-ionizing radiation (ultraviolet rays). Ionizing radiations are of high-energy, and are useful for medical diagnosis because they penetrate the living tissues for substantial distances. In the process, these high-energy rays collide with molecules (directly or indirectly) and cause the release of electrons, leaving positively charged free radicals. The free radicals in turn, collide with other molecules and cause the release of additional electrons and the cycle continues. The ionizing effects of X-rays are related to its mutagenic effects. X-rays cause chromosomal mutations or chromosomal aberrations e.g., chromosomal translocation, breakage of one or both DNA strands (deletion), loss of a base (point mutation), breakage of hydrogen bonds between DNA strands, and cross-linking of DNA strands with other DNA strands.

The major effect of UV rays (non-ionizing radiation) is on the pyrimidines, where dimers are formed, particularly between two thymine residues (Fig. 7.6). It is believed that thymine dimers distort the DNA conformation and inhibit normal replication. The distortion of DNA strand caused by the thymine dimer is recognized and the enzyme DNA photolyase binds to the thymine dimers and cleaves the phosphodiester bonds. DNA polymerase I fills the gap by inserting deoxyribonucleotides complementary to those on the intact strand. The joining enzyme DNA ligase seals the gap that remains at the end

of the last deoxyribonucleotide inserted, closing the gap (Fig. 7.7). With extensive exposure to UV light, this repair system is overwhelmed and skin cancer develops.

Oncogenic Viruses

Both RNA containing and DNA containing viruses have been identified as carcinogenic, both *in vitro* and *in vivo*. There are two common features in their mechanisms of neoplastic induction. Firstly, these viruses incorporate their genetic material (DNA or RNA) into the host DNA, and secondly their genetic material must be expressed in the form of proteins to maintain the host cell in the transformed state.

Four DNA viruses have clearly demonstrated their oncogenic potentials in animals and humans: human papilloma virus (HPV), Epstein-Barr virus (EBV), human herpes virus-8 (HHV-8), and hepatitis B virus (HBV).

Two different types of oncogenic RNA or retroviruses have been recognized based on their ability to induce neoplasms; they include slow transforming virus and acute transforming virus. Most cancer-causing viruses are not very potent at inducing cancer. An organism must be infected for a long period of time before a tumor actually develops.

A typical retrovirus requires three protein-coding genes for the virus life cycle: *gag*, *pol*, and, *env* (Chapter 11). In addition to the life-cycle genes, some retroviruses also carry an oncogene that gives them the ability to transform normal cells into cancerous cells they infect; these are the oncogenic retroviruses. Viral oncogenes (v-*oncs*) are responsible for many different cancers. The v-*onc* genes are named for the tumor that the virus causes, with the prefix "v" to indicate that the gene is of viral origin. Thus, the v-*onc* gene of RSV or Rous sarcoma virus is v-*src* (sarcoma).

Further, most viruses are inefficient or unable to transform normal cells into cancerous cells grown in the laboratory, as they do not contain

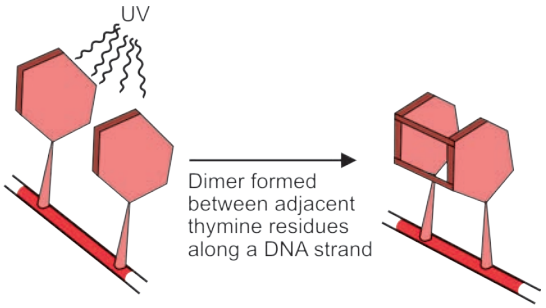

Fig. 7.6: Formation of a thymine dimer

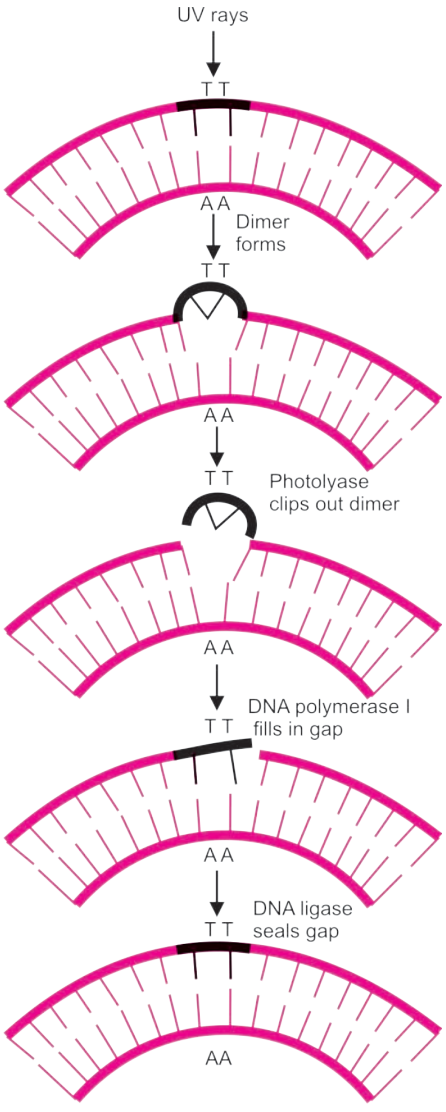

Fig. 7.7: DNA repair

v-*onc*. These are called slow transforming viruses e.g., mouse mammary tumor virus. The slow transforming viruses infect the cells but are unable to produce progeny viruses because of the absence of one or more genes needed for virus reproduction. These defective slow transforming viruses can produce progeny viral particles, if the cell containing them is also infected with a normal virus (helper virus) that can supply the missing genes. This mechanism of transformation is called insertional mutagenesis.

By comparison, some viruses rapidly induce tumors in animals and efficiently transform cells in culture, as they contain v-*onc*. These are called acute transforming viruses e.g., Rous sarcoma virus or Abelson leukemia virus.

The human T cell leukemia virus (HTLV-1) is associated with a form of T-cell leukemia/lymphoma that is endemic in certain parts of Japan and the Caribbean islands. However, the HTLV-1 does not contain v-*onc*. The genome of HTLV-1 contains, in addition to the usual retroviral genes, a unique region called *p*X. This region encodes several proteins, including one called TAX. Upon infecting may T cells the TAX protein causes polyclonal proliferation of T cells and suppresses the function of *p53* tumor suppression gene. Ultimately, a monoclonal T-cell leukemia/lymphoma results when one proliferating T cell suffers additional mutations.

METASTASIS

The mechanism of metastasis is best understood by studying the normal epithelial–connective tissue interface (Chapter 9). The basal lamina is a formidable proteinaceous barrier to tumor cell migration. Oral keratinocyte proliferation is confined initially to the epithelial compartment. Eventually, the proliferating keratinocytes 'break through' the basal lamina and expand through the underlying connective tissue to invade lymph and blood vessels (Fig. 7.8), resulting in distant spread (metastasis). For the purpose of

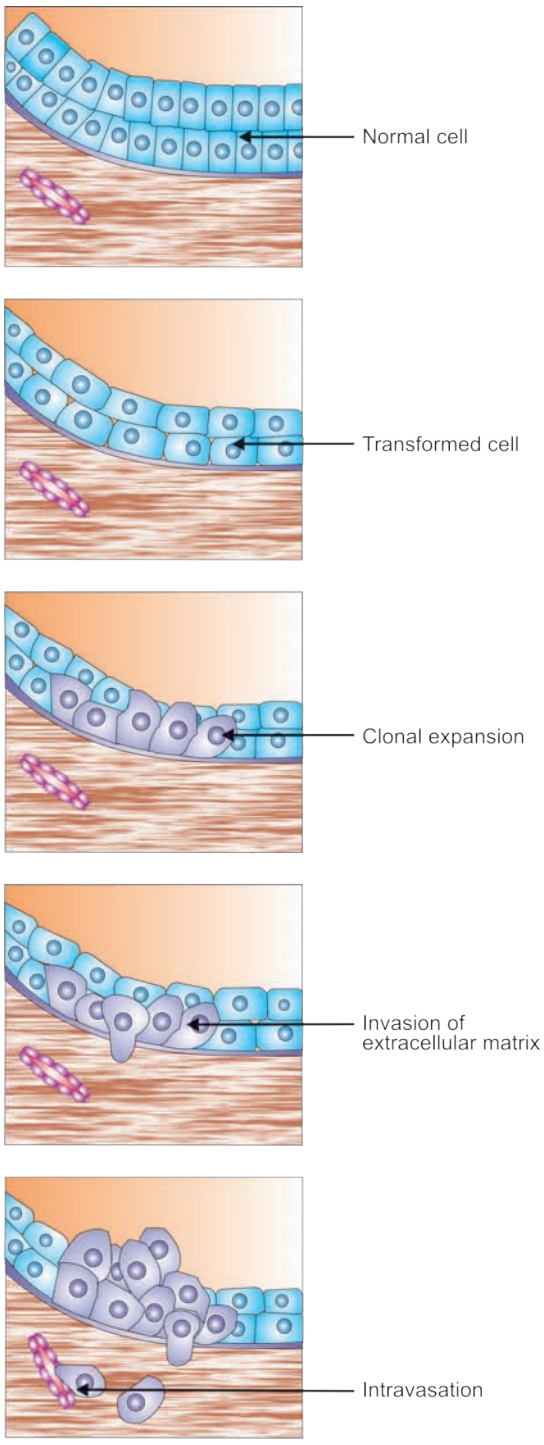

Fig. 7.8: Metastatic cascade

discussion, the metastatic cascade can be subdivided into two phases: invasion of extracellular matrix and vascular dissemination and homing of tumor cells.

Invasion of Extracellular Matrix

1. Looseing of intercellular junctions

The first step in metastasis is loosening of intercellular junctions. E-cadherins act as intercellular glues, and their cytoplasmic portions bind to β-catenin. E-cadherin molecules keep the cells together, and transmit antigrowth signals *via* β-catenin. E-cadherin function is lost in oral squamous cell carcinoma, either by mutation of E-cadherin genes or by activation of β-catenin gene, which can activate transcription of growth factor genes by free β-catenin protein.

2. Attachment

The second step in metastasis is attachment of cancerous cells to the large cruciate glycoprotein, called laminin present in the lamina lucida and fibronectin present in the lamina densa. Normal epithelial cells have receptors at their basal surface for laminin. In contrast, cancerous cells have more laminin receptors and these are distributed all around the cell membrane.

3. Degradation

The third step in metastasis is local degradation of the basal lamina and connective tissue. Cancerous cells penetrate the basal lamina barrier and spread through the underlying connective tissue with the help of matrix protein degrading enzymes called "matrix metalloproteinases' (MMPs). The principal function of MMPs is the proteolytic degradation of connective tissue proteins. MMPs are produced by the cancerous cells themselves or the tumor may stimulate other cells such as fibroblasts in the connective tissue to produce MMPs.

MMPs are secreted in an inactive form and are activated subsequently by other active MMPs called membrane type MMPs (MTMMPs) or mast cell chymase. The MMPs are a family of zinc containing endo-proteinases and the MMP (matrix metalloproteinase) gene family encodes more than 20 different MMPs. MMPs are grouped by their substrate specificity:

i. The collagenases (MMP-1 and MMP-8) cleave collagen I, II and III preferentially
ii. The stromelysins (MMP-3, MMP-10, and MMP-11) cleave laminin
iii. The gelatinases (MMP-2 and MMP-9) cleave type IV collagen

Many other connective tissue proteins are potential substrates of MMPs including elastin, proteoglycans (glycosaminoglycans e.g., dermatan sulfate and heparan sulfate), hyaluronan, fibronectin, and integrins. MMP-1, MMP-2, MMP-3, and MMP-9, are highly expressed in oral cancers and the surrounding connective tissue (especially at the invading front of the tumor) and high levels of MMPs expression may indicate a poor prognosis.

4. Migration

The fourth and final step in metastasis is migration of cancerous cells through the degraded basal lamina and connective tissue. Migration seems to be mediated by tumor cell-derived protein called autocrine motility factor. Autocrine motility factor is a cytokine. Cytokines are low molecular weight proteins, which induce their effects in three ways:

i. They act on the same cell that produces them (autocrine effect)
ii. They effect other cells in their vicinity (paracrine effect)
iii. They effect cells systemically (endocrine effect)

5. Vascular Dissemination and Homing of Cancerous Cells

Once in the circulation the cancerous cells are prone to destruction by the host immune cells

(CD8+ T cells lymphocytes, NK cells, and macrophages). However, most cancerous cells evade the immune system by several escape mechanisms, even in individuals who are immunocompetent. Most cancerous cells circulate as single cells. However, some cancerous cells form embolus by aggregating and adhering to platelets. Extravasation of cancerous cells involves adhesion to the vascular endothelium, followed by migration through the basement membrane by mechanism similar to that involved in invasion. The site of extravasation and homing of the cancerous cells is dependent on the location of the primary tumor and its vascular and lymphatic drainage.

CLINICAL APPEARANCE

Oral cancer has a varied clinical appearance. Most of the lesions can be described as exophytic, ulcerative and verrucous carcinoma.

Exophytic Cancer

The term exophytic is used to describe an outwardly growing tumor. The exophytic lesion (Figs 7.9 A and B) is fixed to the underlying tissues due to its spread. Exophytic cancers metastasize less frequently than the ulcerative type.

Ulcerative

The ulcerative lesion (Fig. 7.10) burrows deep into the mucosa with a breach in the surface. Rolled (everted) margins and induration on palpation, are indicative of a hard tumor mass within the tissue. Ulcerative lesions metastasize more frequently than exophytic cancers.

Verrucous

Verrucous carcinoma (Fig. 7.11) also known as Ackerman's tumor is a distinct clinico-

Fig. 7.9A: Exophytic squamous cell carcinoma

Fig. 7.9B: Exophytic cancer with palatal perforation in reverse *chutta* smoker

Fig. 7.10: Ulcerative squamous cell carcinoma

Fig. 7.11: Verrucous squamous cell carcinoma

pathological variant of squamous cell carcinoma. The term "verrucous" is used because of its fine, finger like surface projections. Verrucous carcinoma represents up to 20% of all squamous cell carcinomas. The characteristic behavior of this carcinoma is its slow growth and rarity to metastasize to the regional lymph nodes. Therefore, it has an excellent prognosis.

DIAGNOSIS

Oral cancer, often presents as a clinical diagnostic challenge to the clinician, particularly in its early stages of development. The most effective way to control oral cancer is early diagnosis and timely and appropriate treatment. The clinician's challenge is to differentiate cancerous lesions from a number of other red, white, or ulcerated lesions that also occur in the oral cavity. Most oral lesions are benign, but may have an appearance that may be confused with a malignant lesion. Conversely, some malignant lesions seen in the early stages may be mistaken for a benign lesion.

Any oral lesion that does not regress spontaneously or respond to the usual therapeutic measures should be considered potentially malignant until proven histopathologically. A period of 2-3 weeks is considered an appropriate period to evaluate the response of a lesion to therapy before obtaining a definitive diagnosis. A definitive diagnosis requires a biopsy. Screening for oral cancer should include a thorough history and physical examination.

History

The first step in screening of oral cancer begins with obtaining demographic data, history of present illness, dental history, medical history, and personal history including tobacco and alcohol abuse. Patients over 40 years of age should be considered at a higher risk for oral cancer.

Physical Examination

The clinician should inspect and palpate the head, neck, oral, and pharyngeal regions. Forceful protraction of the tongue with gauze is necessary to visualize the posterior and lateral aspect of the tongue. In addition, this procedure involves digital palpation of head and neck lymph nodes (Fig. 7.12). A normal cervical lymph node is not palpable on routine examination. In general, tender, soft, enlarged, and freely movable nodes suggest acute infection. Non-tender, hard, enlarged, and fixed nodes suggest chronic infection or malignancy (Fig. 7.13).

The lymph nodes are fixed and non-mobile due to perforation of the nodal capsule and invasion into the surrounding tissue. The lymphatics draining the various anatomical sites in head and neck are located in the specific anatomical locations. To provide health care professional with common terminology, the lymph nodes of head and neck are described by levels (Fig. 7.14).

DIAGNOSTIC AIDS

Useful adjuncts include biopsy (Chapter 2), vital staining, exfoliative cytology, fine needle aspiration biopsy, and diagnostic imaging.

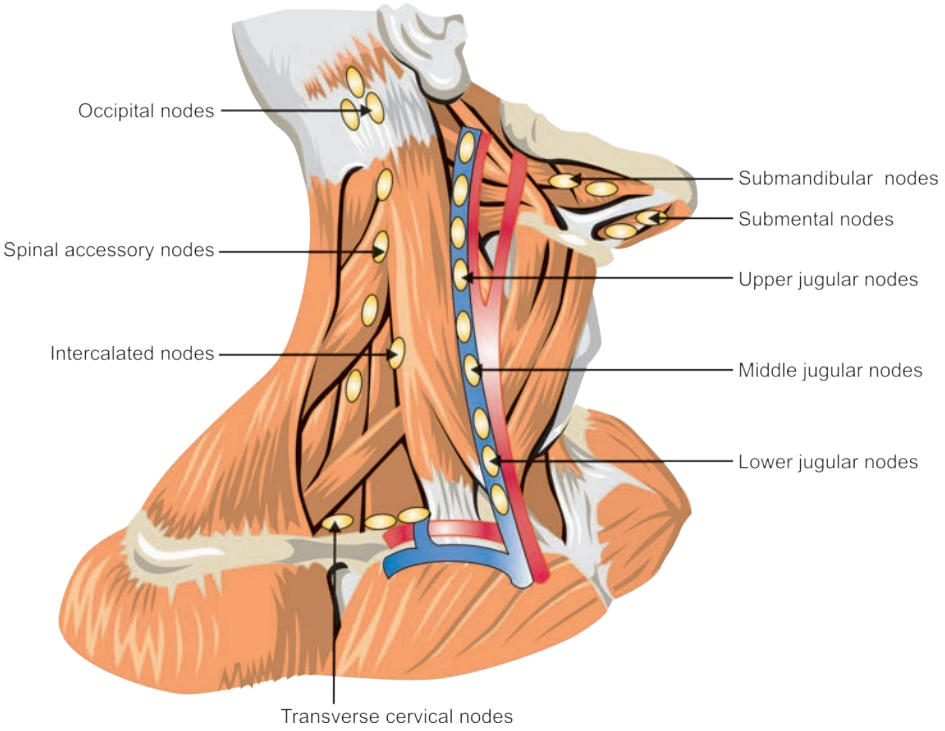

Fig. 7.12: Lymph nodes of head and neck (does not include all nodes)

Fig. 7.13: Non-tender, hard, enlarged and fixed nodes in oral cancer

Vital Staining

In 1963, Richart described an *in vivo* method of staining for dysplasia and carcinoma *in situ* of the cervix. This method has been used for many years to help identify dysplastic or malignant mucous membrane in oral cavity. The classic reported technique involves, drying of the mucosa with gauze and topical application of 1% aqueous solution of tolonium chloride (Toluidine blue) to the suspected lesion for 1 to 2 minutes. A final 1 minute rinse with 1% acetic acid solution for decolorization completes the sequence. If the toluidine blue rinse is, retained malignancy or dysplasia is suspected (Fig.7.15). Vital staining is a useful adjunct in identification of the biopsy site. The fact that false negative results occur in a significant number of cases makes the method unreliable as a diagnostic aid.

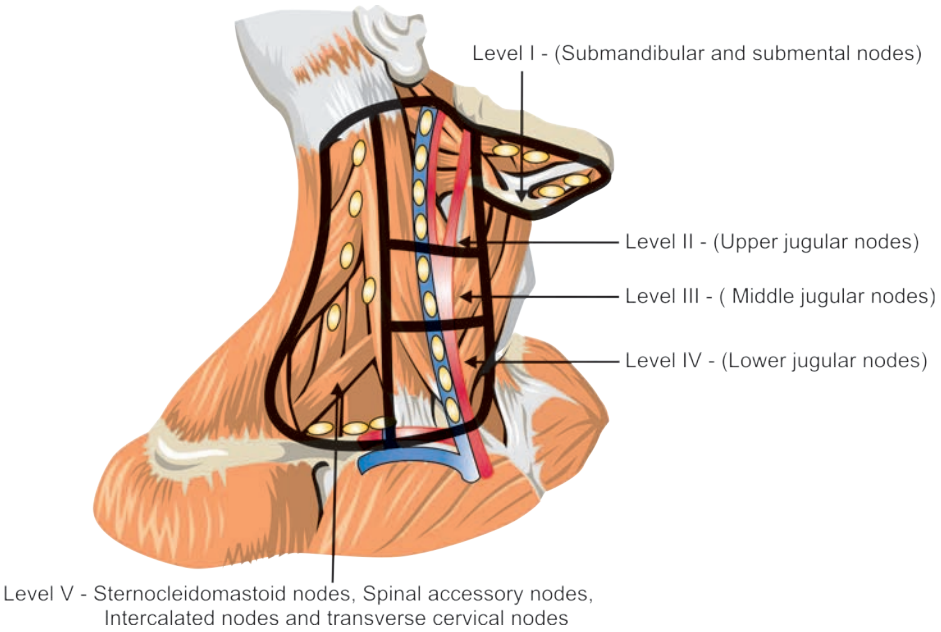

Fig. 7.14: Levels of cervical lymph nodes

Fig. 7.15: Toluidine blue staining

Fine Needle Aspiration Biopsy

Fine needle aspiration biopsy is a quick, inexpensive, accurate, and easy to perform technique that can help in diagnosis of metastasis in enlarged cervical lymph nodes in the patient with oral cancer. A 10 ml syringe, 22-gauge needle, microscope slides, and 95% alcohol for fixation are all that is required. The skin overlying the enlarged lymph node is prepared with iodine and the needle is inserted into the mass. The needle is moved up and down through the mass while maintaining suction at the same time. Suction is released and the needle is withdrawn. One drop of fluid is expressed onto the microscope slide and smeared using another slide, and placed in the alcohol fixative. If there is sufficient material, two or three slides can be prepared. It should be remembered that a negative result does not mean there is no cancer, but a positive result is diagnostic.

Diagnostic Imaging

Diagnostic imaging consists of intraoral radiographs, extraoral radiographs (Figs 7.16A and B), magnetic resonance imaging, computed tomography or optical coherence imaging. Computed tomography is superior in detecting early bone invasion and lymph node metastasis, but magnetic resonance imaging is

Fig. 7.16A: Destruction of mandible due to oral cancer

Fig. 7.16B: Pathological fracture of mandibe due to oral cancer

preferred for assessing the extent of soft tissue involvement and for providing a three-dimensional display of the tumor. Magnetic resonance imaging is also the preferred technique for imaging carcinoma of the nasopharynx or lesions involving paranasal sinuses or the skull base.

HISTOPATHOLOGICAL FEATURES

Squamous cell carcinoma is diagnosed by histopathological examination of the cancerous tissue. A common feature of oral squamous cell carcinoma is the invasion of cancerous cells into the underlying connective tissue, eroding the lymphatic and blood vessel walls and being transported to distant sites.

The potential to metastasize is related to the histopathological variation of oral squamous cell carcinoma. The histopathological variation is related to the degree of differentiation of the cancerous cells and their resemblance to the normal stratified squamous epithelium. The histopathological features of oral squamous cell carcinoma are graded as, well-differentiated,

moderately differentiated, and poorly differentiated. Most oral squamous cell carcinomas are moderately or well-differentiated.

Well-differentiated

Tumors that exhibit individual cell keratinization, keratin pearls and bear resemblance to stratified squamous epithelium are considered as well-differentiated. The epithelial cells are highly dysplastic. There is a break in the basement membrane, and the dysplastic cancerous cells invade the underlying connective tissue, which has dense lymphocyte infiltration. The dysplastic cancerous cells have an architectural pattern and exhibit cohesiveness.

Moderately Differentiated

Tumors that produce little or no keratin but in which the epithelium still is recognizable as stratified squamous are considered as moderately differentiated. The epithelial cells are highly dysplastic. There is a break in the basement membrane, and the dysplastic cancerous cells invade the underlying connective tissue, which has moderate lymphocyte infiltration. The dysplastic cancerous cells have an architectural pattern and exhibit cohesiveness.

Poorly Differentiated

Tumors that produce less keratin, and bear no resemblance to stratified squamous epithelium are considered as poorly differentiated. The epithelial cells are highly dysplastic. There is a break in the basement membrane, and the dysplastic cancerous cells invade the underlying connective tissue, which has minimal lymphocyte infiltration. The dysplastic cancerous cells have no architectural pattern and exhibit lack of cohesiveness.

Variants

Rarely oral squamous cell carcinoma appears as a proliferation of spindle cells. This type of tumor is known as spindle cell carcinoma. Histopathologically verrucous carcinoma is characterized by large, keratinized clefts with bulbous rete pegs that project uniformly into the connective tissue. The keratinized clefts contain parakeratin plugs.

TREATMENT

The management of oral squamous cell carcinoma depends on the tumor's stage. At present, oral squamous cell carcinoma is primarily managed with surgery and radiation therapy. Conventional staging uses the TNM system, in which T stands for tumor, N for nodes, and M for metastasis. This system of staging has been suggested and revised by the International Union against Cancer (UICC, 1987). It has three main parameters: T, N, and M. T classification (Table 7.2) is dependent on the size of the primary tumor. N classification (Table 7.3) depends on both the size and number of involved nodes. M classification (Table 7.4) is the simplest because tumors are classified as either M0 (i.e., show no evidence of metastasis) or M1 (i.e., show evidence of distant metastasis). This classification is then used to divide the tumor into stages (Table 7.5) which has prognostic significance.

In stages I and II either surgery or radiation therapy gives similar prognosis. Therefore, treatment depends on the patients choice, the surgeon's advice, or other factors, such as age, and general medical health. In general, radiation therapy is usually recommended. If radiation therapy fails patients can be saved by surgery.

In stages III and IV, the best cure rates are obtained with a combination of surgery and radiation therapy. Most surgeons's prefer to administer radiation within 6 weeks after surgery. Stage IV disease has the worst prognosis and patients with distant metastasis die.

Complications of Radiotherapy

Ionizing radiation delivered in doses that kill rapidly dividing cancer cells induces unavoidable changes in the surrounding normal

Table 7.2: TNM system: T classification	
T	Primary tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor 2 cm or less
T2	Tumor greater than 2 cm but not greater than 4 cm
T3	Tumor greater than 4 cm
T4	Tumor invades adjacent structures (e.g., through cortical bone, into deep extrinsic muscle of tongue, maxillary sinus, skin)

Table 7.3: TNM system: N classification	
N	Regional lymph nodes
NX	Regional nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less
N2	
N2a	Metastasis in a single ipsilateral lymph node, greater than 3 cm but not greater than 6 cm
N2b	Metastasis in multiple ipsilateral lymph nodes, none greater than 6 cm
N2c	Metastasis in bilateral or contralateral lymph nodes, none greater than 6 cm
N3	Metastasis in a lymph node greater than 6 cm

Table 7.4: TNM system: M classification	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

tissues. The oral mucosa, the salivary glands, and blood vessels can be damaged because of radiotherapy. As a result, patients experience unwanted oral effects during and after radiotherapy. The period between diagnosis of cancer and the commencement of radiotherapy is short. During this period, oral care should be implemented to reduce complications during and after radiotherapy.

Table 7.5: TNM system: Clinical staging			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IV	T4	N0, N1	M0
	Any T	N2, N3	M0
	Any T	Any N	M1

Dental Treatment before Radiotherapy

Oral care includes a radiographic survey of both dentate and edentate patient. The resultant treatment plan should include the appropriate use of 0.2% chlorhexidine mouthwash, and scaling. This will treat any periodontal diseases. Decayed teeth should be restored preferably with a permanent restorative material. Sharp teeth and restorations should be reshaped since they can contribute to soft tissue damage and ulceration. Dentures should be examined and if ill-fitting should be modified. Any necessary dental extractions should be completed at least 10 days prior to commencement of radiotherapy. It should be remembered that asymptomatic periapical lesions are unlikely to be aggravated by radiotherapy.

SEQUELAE OF RADIOTHERAPY

Mucositis

The acute oral mucosal reaction (mucositis) is secondary to radiation-induced death of the basal cells in the oral mucosa. Mucositis commences within 12 to 15 days after radiotherapy starts. It is characterized by large areas of desquamation

and ulcerations. The patient needs to be constantly reassured that this condition is temporary.

Management of mucositis includes application of topical anesthetics (2% lignocaine), 0.2% chlorhexidine mouthwash gargles, frequent sipping of cold water, and holding of ice cubes in the mouth. A short course of systemic prednisolone (40 to 80 mg for not more than 1 week) may be helpful in reducing inflammation.

Loss of Taste

Taste buds, which occur primarily in the circumvallate and fungiform papillae, are very sensitive to radiation. Because of their location in the tongue, they are included in the beam of radiation for most oral cancers. Therefore, patients will develop a partial (hypoguesia) or complete (aguesia) loss of taste sensation during radiotherapy. The cells of the taste buds usually regenerate within 4 months after therapy.

Xerostomia

Exposure of the major salivary glands to ionizing radiation induces fibrosis, fatty degeneration, acinar atrophy, and cellular necrosis within the glands. The serous acini appear to be more sensitive than the mucous acini. The saliva is thick, sticky, and bothersome. The duration of depressed salivary function varies from patient to patient. However, the depressed salivary function may take upto 12 months.

Management of xerostomia includes frequent sipping of cold water, holding of ice cubes in the mouth, chewing sugar-free gums, and lubrication with saliva substitutes. It is often difficult to sleep at night when the mouth is dry, butter wiped on lips and tongue prior to sleeping can be helpful.

Nutrition

Because of mucositis, loss of taste, and xerostomia, the desire not to eat is a common complaint in patients receiving radiotherapy. A resultant weight loss tends to produce weakness, inactivity, and susceptibility to infection. Therefore, close attention is given to food intake and weight maintenance during and after therapy.

Dental Caries

Patients who have not shown any caries activity for years may develop caries during radiotherapy. The cervical areas are most commonly affected. This condition appears due to the lack of saliva as well as change's in the saliva's chemical composition.

The 0.2% chlorhexidine mouthwash gargles and daily applications of topical fluoride are essential to prevent or at least minimize radiation caries. Food and beverages containing sucrose should be avoided. Restorations of the carious teeth should take place immediately.

Oral Candidosis

Oral candidosis is commonly seen in patients who have been receiving radiotherapy. This condition appears due to the lack of saliva as well as change's in the saliva's chemical composition. Management is accomplished with topical and systemic antifungal drugs.

Trismus

Ionizing radiation causes obliterative endarteritis resulting in tissue ischemia and fibrosis. Obliterative endarteritis can contribute to the development of trismus if the masticatory muscles are within the beam of radiation. Management of trismus can be very difficult. Jaw exercises using tongue blades may be helpful.

Osteoradionecrosis

Osteoradionecrosis or post-radiation osteoradionecrosis (PRON) is a painful and debilitating serious complication of radiotherapy. Radiation

of the jaws in excess of 50 Gy kills bone cells and causes a progressive obliterative arteritis (endarteritis, periarteritis, hyalinization, fibrosis, and thrombosis of vessels), resulting in aseptic necrosis of the bone within the beam of radiation. Effective response to infection is reduced to a great extent. It should be remembered that microorganisms are merely contaminants in osteoradionecrosis.

Osteoradionecrosis is a radiation-induced hypoxia, hypocellularity, and hypovascularity of the bone forming cells. Pain and exposed bone (gray to yellow color) are the chief clinical features of osteoradionecrosis of the jaws. Other clinical features of osteoradionecrosis include trismus, halitosis, and pyrexia with extraoral and intraoral sinuses. Radiographic features include pathological fracture and formation of sequestra or involucra.

The mandible is affected more commonly than the maxilla because most oral tumors are perimandibular. Also, the absence of dense cortical plates and the presence of extensive vascular network in the maxilla decreases its probability of radiation necrosis compared with the mandible. The risk is increased in dentate patients if the teeth within the beam of radiation are removed after radiotherapy. Other risk factors include mucosal ulcers, lacerations, scaling, fractures, periodontal disease, and careless root canal therapy.

Extractions following radiotherapy should be done with minimal trauma along with soft tissue closure. The use of 0.2% chlorhexidine mouthwash prior to extraction can reduce bacterial flora and improve healing. In case of multiple extractions, hyperbaric oxygen therapy is recommended before and after extraction.

Administration of antibiotics together with excision of necrosed bone and hyperbaric oxygen (HBO) therapy may be helpful. Hyperbaric oxygen therapy consists of breathing 100% oxygen through a face mask in a large chamber at 2 to 2.5 absolute atmospheres pressure for 1.5 to 2 hours sessions or "dives" per day. Upto 80 sessions have been recommended for severe cases but chambers are often small, and claustrophobic. HBO therapy causes an increase in arterial and venous oxygen tension; the additional oxygen is carried into the plasma. Oxygen under increased tension enhances healing by a direct bacteriostatic effect on microorganisms that renders them susceptible to lower antibiotic concentrations and phagocytosis. In addition, neoangiogenesis, fibroblastic proliferation, and collagen synthesis occur. There have been promising results recently with ultrasound at frequencies of 3 MHz pulsed 1 in 4 at an intensity of 1 w/cm sq. applied to the mandible.

CANCER CACHEXIA SYNDROME

The term cachexia is derived from the Greek word *kakos* meaning "bad" and *hexis* meaning "condition." Cancer cachexia syndrome is characterized by anorexia (lack of desire to consume food), weight loss, marked muscle weakness, anemia of nonspecific type, impaired immune function due to increase nutritional demands of the tumor, increased energy expenditure of the cancer patient, and improper use of nutrients by the cancer host. There is no satisfactory treatment for cancer cachexia syndrome other than removal of the underlying cause, i.e., the tumor.

FUNCTIONAL REHABILITATION

The cosmetic, functional, and psychosocial effects of oral cancer treatment may combine to produce devastating effects on patients, especially if the tumor is extensive or if the treatment is aggressive. Various functions are affected, which include speech, mastication, and deglutition.

Functional rehabilitation is directly related to the location and extent of the cancer and the type of surgery and radiation therapy used. Successful functional rehabilitation and quality of life go hand in hand.

Functional rehabilitation is a multidisciplinary approach. Maxillofacial prosthetic rehabilitation is the basis to restore the patients oral functions and cosmetics following surgery. Other health care professionals including psychologist, occupational therapist, physiotherapist, speech therapist, and dental hygienist are also members of functional rehabilitation team.

The patient with a total maxillectomy is the most difficult to treat prosthetically as well as emotionally. The fabricated prosthesis is usually less satisfactory to the patient. The patient with a partial maxillectomy is much easier to treat. Generally, maxillofacial prosthodontists restore maxillary resections with obturator prostheses. Patients with lesions involving the soft palate, which requires surgical excision, need an obturator with soft palate extension in order to restore speech.

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Chapter 8

Oral Candidosis

HISTORY

Hippocrates described oral candidosis in his treatise (piece of writing) *Epidemics*, which was published in the 4th century B.C. The first research on oral candidosis was carried out in the year 1786 in France. Berkhout in 1923 proposed the term candida that in Latin means *toga candida* referring to white robe worn by Roman senates. Albicans also comes from Latin word *albicare*, which means, "to whiten." Rippon has suggested that candidosis is European in origin whereas candidiasis is basically American in origin. However, according to Odds either term is acceptable but candidosis is more preferred term.

Microbiology

It is one of the most common fungal infections of man. At least 90 genera and 90 species have been isolated from the human beings few of them are *Candida tropicalis*, *Candida pseudotropicalis*, *Candida albicans*, and *Candida glabrata*. *Candida albicans* is a normal commensal of the oral cavity and lives harmoniously with the other microbial flora but when the immunity of the host is suppressed or there are any predisposing factors it proliferates and penetrates the tissue to cause candidosis.

Candida albicans is most commonly found on the tongue, palate, and buccal mucosa. It has also been isolated in high concentration from tissue bearing surfaces of removable appliances. The yeast candida can be inoculated in the mouth of newborn during birth, breast feeding, pacifiers and nurse's hands. Audrey in 1887 described the morphology of *Candida*. Morphologically *Candida albicans* exists in three forms Yeast form (blastospores), Pseudohypha and Chlamydospore (Fig. 8.1). It multiplies by division of blastospores.

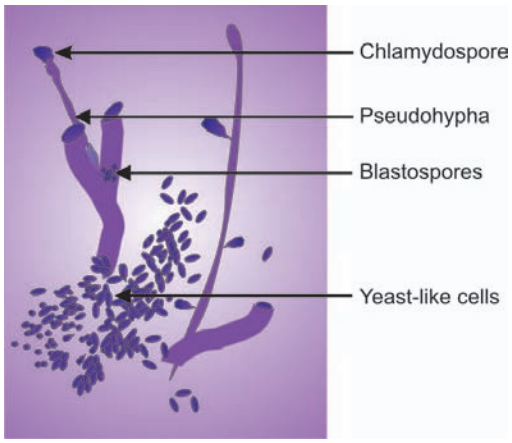

Fig. 8.1: Morphology of *Candida albicans*

Predisposing Factors

The various factors that predispose to an individual oral candidosis are as follows:

Palatal appliances: Local trauma from ill-fitting dentures and poor denture hygiene are important predisposing factors in the etiology of oral candidosis.

Heavy smoking: In heavy smokers, the phagocytosis and the bactericidal activity of PNML are impaired.

Xerostomia: Sjögren syndrome, medications (e.g., anti-depressants), radiation therapy, surgical removal of salivary glands cause xerostomia as a result of which the defense mechanism of saliva and the levels of salivary IgA is diminished or absent.

Steroid inhalers: Long-term use of steroid inhalers can induce oral candidosis because corticosteroids suppress the immunity. Hence, it is advisable to gargle after the use of steroid inhaler.

Pregnancy: During pregnancy, there is gestational diabetes mellitus, which may predispose the oral cavity to candidosis. Causes of diabetes mellitus in pregnancy are as follows:

1. Increased absorption of glucose from alimentary tract
2. Inability of insulin to convert glucose into glycogen
3. Impaired tubular reabsorption of glucose which leads to glycosuria

The other predisposing factor during pregnancy is iron deficiency anemia.

Broad spectrum antibiotic therapy: As the normal flora are suppressed and destroyed during treatment with broad spectrum antibiotics, the colonization of oral cavity with *Candida* may be significantly increased.

Nutritional factors: Deficiency of iron, folic acid, vitamin B_{12} and carbohydrate-rich diet can predispose an individual to oral candidosis. The various possible mechanisms by which iron deficiency can predispose to oral candidosis are as follows:

1. Epithelial abnormalities because of iron dependent enzyme systems
2. Depression of cellular immunity
3. Inadequate antibody response
4. Deficient phagocytosis

Vitamin deficiency usually affects the integrity of the oral mucosa by altering the cellular metabolic pathways thus predisposing the oral mucosa to candidosis. For an organism like *Candida albicans*, the most important thing is to adhere to epithelium or the denture. Recent studies have shown that this adherence is enhanced in the presence of carbohydrates like glucose and sucrose.

Uncontrolled diabetes mellitus: In diabetes mellitus there is defective PMNL function, increased glucose in saliva and polyuria that leads to xerostomia. All these are ideal predisposing factors.

Acquired immune deficiency syndrome: The main cause of oral candidosis in AIDS is because of decreased CD4 cell count, side effects such as xerostomia due to didanosine (anti-retroviral drug), and other antibiotics taken to treat or prevent HIV-related conditions.

Leukemia: Neutropenia and cancer chemotherapy predisposes to oral candidosis.

Defense Mechanisms

The four important defense mechanisms that play a role against *Candida albicans* are:

Secretory IgA: Minor salivary glands secrete more IgA than major. Mechanism of action of secretory IgA is that it prevents the adhesion of *Candida albicans* to oral mucosa.

Saliva: Major salivary glands secrete more saliva than minor salivary glands. Mechanism of action of saliva is that it dislodges microorganisms from the surface of the mucosa and has the following factors like lysozyme, lactoperoxidase, histatins, lactoferrin, and calprotectin, which inhibits the growth of various *Candida* species *in vitro*. Lactoferrin a chelating agent competes with the *Candida albicans* and other microorganisms of the oral cavity for free iron radicals that are apparently essential for bacterial and fungal multiplication.

PMNL and macrophages: PMNL and macrophages phagocytose and kill *candida* even in the absence of specific opsonizing antibodies, though their activity is enhanced when such antibodies

are present. However, in heavy smokers, diabetes mellitus, and Chediak-Higashi syndrome there is defective PMNL function.

CLASSIFICATION

Acute

1. Pseudomembranous
2. Atrophic

Chronic

1. Atrophic
2. Hyperplastic

Candida-associated Lesions

1. Angular cheilitis
2. Median rhomboid glossitis

HIV-associated Candidosis

1. Erythematous
2. Pseudomembranous
3. Mixed

Chronic Mucocutaneous Candidosis

1. Localized (mucosa, nails, skins)
2. Familial
3. 1. Endocrinopathy syndrome (hypopara thyroidism, Addison's disease, and hypothyroidism)

Acute Pseudomembranous Candidosis

Acute pseudomembranous candidosis is also known as thrush. It forms white plaques (Fig. 8.2) or flecks, which can be scrapped off. Scrapping these white plaques leaves a raw bleeding surface. These plaques are made up of necrotic material composed of desquamated epithelial cells. They often misguide the clinician for a mistaken diagnosis of oral leukoplakia. Angular cheilitis may or may not be associated. It is seen in young, elderly, and debilitated patients.

Acute Atrophic Candidosis

Acute atrophic candidosis is also known as antibiotic sore mouth because it frequently occurs during long-term antibiotic therapy. There are no plaques in acute atrophic candidosis. However, there is severe burning sensation.

Fig. 8.2: Acute pseudomembranous candidosis

Chronic Atrophic Candidosis

Chronic atrophic candidosis is also known as denture sore mouth. It is the most common form of oral candidosis with a strong female predilection. Patients who wear their appliances in day and night are prone to it. Classically the lesions are seen on the denture bearing palatal mucosa and are erythematous and asymptomatic. The etiology of this lesion was not known properly until mid 1960's until Cawson's studies. Prior to which it was thought that etiology of chronic atrophic candidosis was due to poor denture hygiene, mechanical irritation, allergy to some component of the denture base material, and irritation from leaching of monomer from an incompletely cured denture.

Etiology

Candida albicans adheres to the denture and produces pyruvates and acetates, which decrease the pH. These metabolites cause inflammation of the palatal mucosa.

Classification

Newton (1962) classified denture sore mouth into three clinical types:

1. Localized simple inflammation
2. Generalized simple inflammation
3. Inflammatory papillary hyperplasia (involving hard palate and alveolar ridge)

Treatment

1. Avoid wearing the denture at night
2. Wash the denture with soap and water
3. Clean the denture with chlorhexidine gluconate 0.20% solution
4. Soak the denture in hypochlorite solution

Chronic Hyperplastic Candidosis

Chronic hyperplastic candidosis was previously termed hyperplastic candidosis or candidal leukoplakia. It is most commonly observed on the buccal mucosa, tongue, and palate. Speckled leukoplakia accounts for 3-50% of all chronic hyperplastic candidosis and is symptomatic. The risk of malignant transformation of chronic hyperplastic candidosis is 9-40%, in comparison to 2-6% risk of malignant transformation for leukoplakias. When biopsy is taken and the lesion examined, it shows parakeratinization, invasion of parakeratin by *Candida albicans*, varying dysplastic features, epithelial hyperplasia, neutrophilic microabscess (Munro abscess), and elongation of rete pegs. Whether oral cancer will develop from chronic hyperplastic candidosis purely depends upon whether the lesion is speckled or homogenous.

Chronic Mucocutaneous Candidosis

The first case of chronic mucocutaneous candidosis or CMC was reported by Forbes in 1909 in a three and half year old girl who had lesions of oral cavity and fingernails. CMC is basically due to defective cell mediated immune response. Lesions of CMC involve skin, mucosa, and nails. There are reports of CMC associated with endocrinopathies like hypoparathyroidism, hypothyroidism and Addison's disease.

CANDIDA ASSOCIATED LESIONS

Angular Cheilitis

Angular cheilitis is also known as perleche or angular stomatitis. The etiology is multifactorial in origin and affects the angles of the mouth, either unilaterally or bilaterally especially in denture wearers. Angular cheilitis can be present in the absence or presence of oral candidosis. The various etiological factors that are associated with angular cheilitis are as follows:

1. Infection with *Candia albicans and Staphylococcus aureus*
2. Iron deficiency anemia
3. Vitamin B_{12} deficiency
4. Decreased vertical dimension resulting in skin creases at the angles of the mouth

Treatment

1. Remove the underlying predisposing factors
2. When there is superadded candidal infection, topical amphotericin (paste or ointment) or nystatin (ointment) should be applied 4 times a day for 4 weeks
3. When *Staphylococcus aureus* is isolated from the angles, fusidic acid cream should be applied 4 times a day for 4 weeks

Median Rhomboid Glossitis

Median rhomboid glossitis is also known as midline glossitis, glossal central papillary atrophy. It is characterized by atrophy of central area of tongue (Fig. 8.3). The atrophy is found anterior to circumvallate papillae (characteristically at the junction of the anterior two thirds and posterior one-third of the tongue) and is rhomboid in shape. Initially median rhomboid glossitis was thought to be a developmental disturbance (defective involution of tuberculum impar). However, in 1965 Cerncea et al found that a high percentage of median rhomboid glossitis has superficial *Candida albicans*.

However, the debate continues as to whether *Candida albican*s causes median rhomboid glossitis or is simply an opportunistic organism that invades tissue that has been altered through other mechanisms.

Fig. 8.3: Median rhomboid glossitis

Diagnosis

To make a diagnosis of oral candidosis, one must be able to see hyphae or pseudophyphae. The most straightforward diagnostic approach is a tissue biopsy stained with periodic acid-Schiff (PAS) stain. Alternatively a sterile cotton swab is used to scrape the lesion, following which the swab can be streaked on the surface of a Sabouraud's agar plate. *Candida albicans* will grow as creamy-white colonies after 2 to 3 days of incubation.

Differential Diagnosis

1. Traumatic ulcers
2. Chemical burns
3. Leukoplakia
4. Mucous patches of syphilis
5. Erosive lichen planus – (acute atrophic candidosis)

Treatment

The main aim in the treatment of oral candidosis is concerned is to primarily detect and remove the predisposing factor or factors followed by anti-fungal therapy if necessary. Anti-fungal drugs are mainly classified into two groups:

Local

1. Clotrimazole 1% w/v –Candid Mouth paint 15 ml
2. Clotrimazole 1% w/v –Nifugal Mouth paint 15ml
3. Clotrimazole 1% w/v–Travoral Mouth paint 15 ml
4. Nystatin tablets–These tablets can be sucked in the mouth and act locally

Systemic

1. Fluconazole tablets 50, 100, 150, 200 mg
2. Amphotericin B tablets 50, 100 mg
3. Itraconazole tablets 100 mg
4. Frequent use of fluconazole leads to resistance especially when treating HIV patients
5. When lesions are resistant to fluconazole the drug of choice is itraconazole
6. Itraconzole interacts with anticoagulants, hypoglycemic drugs and is contraindicated in pregnancy. Thus, it should be prescribed with care.

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Chapter 9

Vesiculobullous and Ulcerative Lesions

INTRODUCTION

The most common vesiculobullous conditions of the oral and perioral soft tissues are viral infections, especially herpes simplex, but also varicella zoster (chicken pox or shingles). In normal immunocompetent patients, these self-limiting conditions resolve spontaneously, usually within days.

Oral erythema multiforme is a mucocutaneous vesiculobullous disease that usually heals spontaneously within 2 to 3 weeks. Several clinical forms occur, including major and minor types. The minor forms involve the skin, with characteristic "target" or "bull's eye" lesions, and the oral mucous membrane. The major types include Stevens-Johnson syndrome, an acute form occurring in young individuals, and toxic epidermal necrolysis both of which are characterized by large bulla formation.

Some rare hereditary forms of vesiculobullous diseases, such as epidermolysis bullosa, usually have onset in infancy. Bullous lichen planus is a rare vesiculobullous variant of lichen planus. Other vesiculobullous conditions, such as contact or systemic allergic reactions, bullous pemphigoid and linear IgA disease, more commonly affect the skin. Pemphigus vulgaris and mucous membrane pemphigoid (MMP) are the two most common mucocutaneous autoimmune bullous diseases that cause chronic oral blistering.

PEMPHIGUS VULGARIS

Pemphigus vulgaris is a mucocutaneous autoimmune bullous disease. There are several types of pemphigus (such as vulgaris, foliaceus, vegetans, IgA pemphigus, herpetiform pemphigus, and paraneoplastic pemphigus); however 80% of all patients have pemphigus vulgaris. Drug induced pemphigus vulgaris-like lesions are known to be caused by D-penicillamine, but similar lesions have also been reported for captopril, phenacetin, furosemide, penicillin, tiopronin and sulfones such as dapsone.

Before systemic corticosteroids were available, the disease was often fatal. Pemphigus vulgaris affects the oral mucosa in nearly all cases and more importantly, the oral mucosa is the site of the first lesion in the majority of cases. Two immune variants are recognized: the mucous membrane predominant type (anti-desmoglein 3 only) and the mucocutaneous type (anti-desmoglein 1 and 3). In the mucocutaneous type, oral ulcerative lesions are often seen before the disease affects the skin. The disease is less common than mucous membrane pemphigoid (MMP), occurring in about 0.1–0.5 patients per 100,000 population a year.

Normal Desmosomes

The pathogenesis of pemphigus vulgaris can best be understood by studying the structure of a

desmosome (Fig. 9.1). Adjacent keratinocytes share a number of attachment junctions including tight junctions, gap junctions, and desmosomes. Desmosomes constitute the primary attachment junctions between adjacent keratinocytes. The tonofilaments or intermediate keratin filaments of each cell are inserted to specialized intracellular thickenings known as desmosomal or attachment plaque. The attachment plaque contains proteins desmoplakin I, desmoplakin II, and plakogloblin. These proteins are linked to desmoglein 3 and desmocollin, which extend through the cell plasma membrane to a widened zone between the two cells called the desmoglea. Within the desmoglea, the desmogleins 3 and desmocollins of adjacent keratinocytes join by homophilic binding to link the two cell membranes together. The expression of desmogleins varies between oral epithelium and skin: oral epithelium contains mostly desmoglein 3, whereas skin contains both desmoglein 3 and desmoglein 1.

Pathogenesis

Serum from patients with pemphigus vulgaris contain circulating autoantibodies (IgG) directed against desmoglein 3. Circulating autoantibodies (IgG) are detectable in 80 to 90% of patients with pemphigus vulgaris, and the titer is generally correlated with severity of clinical disease.

Pemphigus vulgaris is caused by type II hypersensitivity reaction. It is likely that C1 protein of complement system binds to antigen-antibody complex (desmoglein 3-IgG) resulting in activation of classical complement pathway and formation of the (MAC) membrane attack complex (C5b, 6, 7, 8 $(C9)_n$). The MAC is a cylindrical transmembrane channel which allows the influx of Na^+ and H_2O due to high internal colloid osmotic pressure, which eventually causes cytolysis of keratinocytes.

Clinical Features

Pemphigus vulgaris affects both sexes equally and is more common among Ashkenazic Jews.

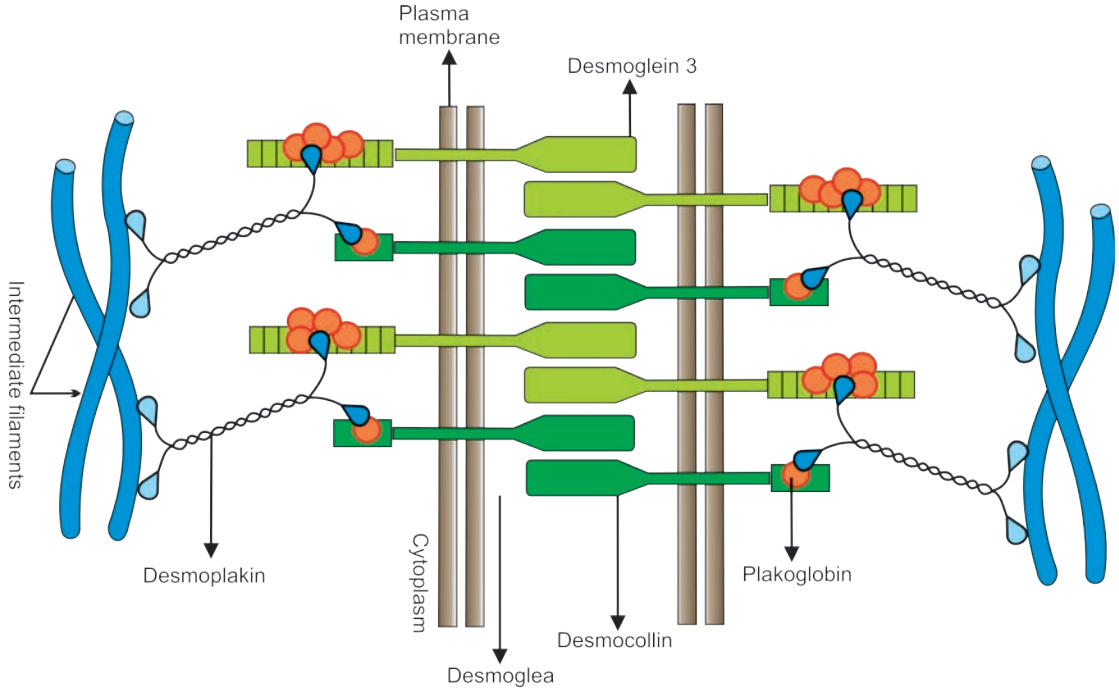

Fig. 9.1: Structure of desmosome

Pemphigus vulgaris most commonly develops during the 5th to 7th decade of life, although rare pediatric cases have been reported.

Clinical Presentation

Since the desmosome is the primary attachment mechanism between keratinocytes, the inflammatory destruction of desmosome leads to the development of characteristic fluid filled bullae. The bullae quickly rupture, leaving a relatively nonspecific, shallow ulceration with an irregular border (Figs. 9.2A to C).

Patients complain of painful, persistent ulcers and sloughing, which may affect any part of the oral cavity but is commonly seen first in the buccal mucosa, palatal mucosa and lips. The ulcerations may affect other mucous membranes, including the conjunctiva, nasal mucosa, pharynx, larynx, esophagus and genital mucosa, as well as the skin where intact bullae are more commonly seen.

When the epithelial attachment is destroyed, even minor mucosal trauma may result in acantholysis, and bullae formation. Therefore, the formation of trauma-induced bullae is one diagnostic tool (Nikolsky's sign) used in assessing the patient who has mucocutaneous bullous disease such as pemphigus vulgaris or mucous membrane pemphigoid. Bulla or ulcer formation after gentle horizontal pressure is applied to the oral mucosa is known as Nikolsky's sign.

Diagnosis

The definitive diagnosis of pemphigus vulgaris cannot be based solely on clinical examination, as several other oral vesiculobullous lesions have a similar appearance (bullous lichen planus, pemphigoid and erythema multiforme). An incisional biopsy containing normal intact epithelium as well as tissue from the area of the ulceration is required for a definitive diagnosis.

Fig. 9.2A: Pemphigus vulgaris with multiple ulcers on the right buccal mucosa

Fig. 9.2B: Pemphigus vulgaris with large irregular shaped ulcer involving the right lateral surfa

Fig. 9.2C: Pemphigus vulgaris with ulceration of the tip of the tongue

The characteristic histopathological features of pemphigus vulgaris include intraepithelial cleft, acantholysis, and a dense mononuclear lymphocytic infiltration in the underlying connective tissue (Fig. 9.3). A simple smear taken from a lesion can also be used to identify acantholytic cells called Tzanck cells which are indicative of pemphigus vulgaris. However, Tzanck cells can also be found in diseases such as herpes simplex, carcinoma, and transient acantholytic dermatosis and therefore are not diagnostic.

The autoantibodies can be detected in the epithelium using direct immunofluorescent staining techniques. Direct immunofluorescent staining technique reveals IgG deposits along the cell membrane of kertinocytes, producing a characteristic "spider-web" or "chicken-wire" or "fish-net" pattern. When this technique is used, a special preservative medium is essential such as Michel's transport medium (pronounced mee-SHELL). Michel's transport medium is used to transport specimens for immunofluorescence studies. It is not a fixative, and is not suitable for any other use (particularly, it is not suitable for transporting living cells for flow cytometry). It should be stored (refrigerated and not frozen) until use. Fixation in formalin will destroy the antigen proteins and render the immunofluorescent staining technique useless.

Treatment

Any patient diagnosed with pemphigus vulgaris or mucous membrane pemphigoid should undergo an ophthalmologic examination to determine if there is any ocular disease. Both of these diseases can result in severe corneal desquamation and conjunctival adhesions, or symblepharon, between bulbar and palpebral conjunctivae, thus causing functional blindness. The patient also should be evaluated for the presence of skin lesions by a dermatologist.

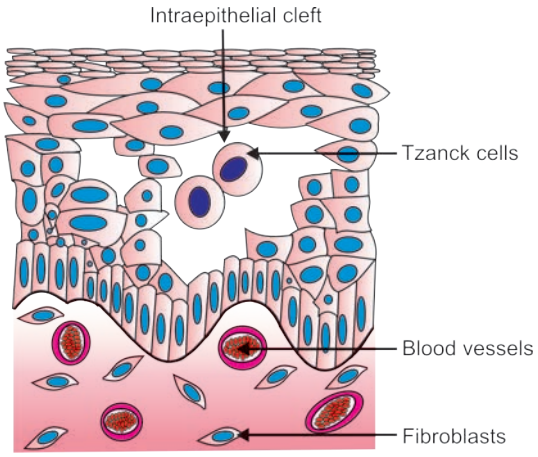

Fig. 9.3: Intraepithelial cleft in pemphigus vulgaris

Mild localized lesions of oral mucous membrane pemphigus may be controlled with topical corticosteroid creams. Intralesional triamcinolone acetonide may be used for resistant local lesions of oral mucous membrane. However, patients with severe localized lesions of oral mucous membrane require systemic corticosteroids, typically starting at 60–80 mg prednisolone a day. If no control is obtained in the first week, the dose is increased to 120 mg a day for a week, then up to 240 mg a day if necessary to prevent new bullae. Once control is achieved, the dose is reduced by half, to 120 mg a day for a week, and then to 80 mg a day for a week until a level of 40 mg a day is reached. The dose is then decreased every 4 months. In most cases, low maintenance doses, usually every other day, are needed for years.

High doses of corticosteroids may be delivered for relapsing or resistant cases, either orally or intravenously ("pulse corticosteroid treatment"). Pulse corticosteroid treatment refers to the intravenous administration of 1 gm/day of prednisolone, or its equivalent, over a period of 1–3 hours, for several consecutive days. The goal of this approach is to quickly achieve the immunosuppressive effects of corticosteroids,

while avoiding the long-term side effects associated with oral administration. It is well-tolerated in young and healthy patients, but may result in serious complications in those suffering from chronic disease. These include severe electrolyte imbalances, hypertension, pancreatitis, seizures, and cardiac arrhythmias. Patients often become cushingoid, and deaths are more often attributed to side effects of corticosteroids than to the disease itself.

Most patients with pemphigus vulgaris receive a second immunosuppressant drug to achieve a complete remission. The most common drug combination is prednisolone with azathioprine, chlorambucil, cyclophosphamide, cyclosporine, methotrexate, and mycophenolate mofetil. These drugs not only provide additional immunoregulatory benefit, but also have steroid-sparing properties that allow the dose of prednisolone to be reduced significantly and complete remission with fewer side effects. The other therapeutic agents now being tried include:

Anti-inflammatory Drugs

1. Gold
2. Dapsone
3. Nicotinamide
4. Tetracycline

Immunomodulatory Procedures

1. Plasmapheresis
2. Extracorporeal photopheresis
3. Human intravenous immunoglobulin (IVIG)

PARANEOPLASTIC PEMPHIGUS

Paraneoplastic pemphigus is a rare vesiculobullous disease of sudden onset of the skin and mucous membranes and always affects the oral mucosa. Oral lesions are very painful and consist of widespread, irregular shallow ulcers at multiple oral sites. Characteristically, they extend on the vermilion border causing hemorrhagic crustations. This condition is seen in elderly patients who usually have a malignancy, typically a lymphoma or chronic lymphocytic leukemia.

CHRONIC DESQUAMATIVE GINGIVITIS

Chronic desquamative gingivitis is a non-specific clinical term that is characterized by fiery red, glazed, atrophic or eroded looking gingiva. There is loss of stippling and the gingiva may desquamate easily with minimal trauma. In comparison to plaque induced gingivitis, chronic desquamative gingivitis is more common in middle-aged to elderly females. Chronic desquamative gingivitis predominantly affects the buccal attached gingiva and sometimes adjacent alveolar mucosa and frequently spares the marginal gingiva. Pemphigus, pemphigoid, erosive and atrophic lichen planus, lupus erythematosus, linear IgA disease, dermatitis herpetiformis, chronic ulcerative stomatitis, graft-versus-host-disease, erythema multiforme, epidermolysis bullosa, plasma cell gingivitis, psoriasis, and Crohn's disease are the entities that may be included under this heading. Its clinical appearance is not altered by traditional oral hygiene measures or conventional periodontal therapy.

MUCOUS MEMBRANE PEMPHIGOID

Mucocutaneous diseases, which are characterized by separation of epithelium from connective tissue, involve alterations in one or more of the anchoring proteins caused by genetic abnormalities (e.g., hereditary epidermolysis bullosa) or autoantibodies. MMP is the most common mucocutaneous autoimmune bullous disease to affects the oral cavity. In the past, MMP was known by several terms, including "benign mucous membrane pemphigoid," "cicatricial pemphigoid" and "ocular or oral–gingival

pemphigoid." However, in the first international consensus on mucous membrane pemphigoid, the term "mucous membrane pemphigoid" was recommended. MMP is defined as an oral disease that rarely or perhaps never involves the skin. Orally, it primarily affects the gingiva (desquamative gingivitis) but may involve any area.

Normal Epithelial-Connective Tissue Interface

The pathogenesis of MMP can best be understood by studying the normal epithelial-connective tissue interface. The region where the connective tissue meets the overlying oral epithelium is known as basement membrane zone (BMZ). Ultrastructurally basement membrane zone is described as basal lamina and is highly organized (Fig. 9.4). The basal lamina consists of a superficial, thin electronlucent zone layer, called the lamina lucida and a deep, granular, electron-dense layer, called lamina densa.

The lamina lucida contains, the bullous pemphigoid antigen 2 or BPAg2 (a180-kD protein), and a large cruciate glycoproteins, called laminin 5 (epiligrin, kalinin, nicein, uncein) and laminin 6. The lamina densa contains proteins such as fibronectin and type IV collagen arranged in a chickenwire configuration. The proteoglycan heparan sulfate coats both surfaces of the lamina densa. Inserted into the lamina densa are small loops called anchoring fibrils, which consists of type VII collagen. Collagen fibrils consisting of type I and type III collagen run through these loops and are interlocked.

Intermediate keratin filaments are bound to hemidesmosome plaque proteins, such as bullous pemphigoid antigen 1 or BPAg1 (a 230-kD protein), and plectin which are in turn

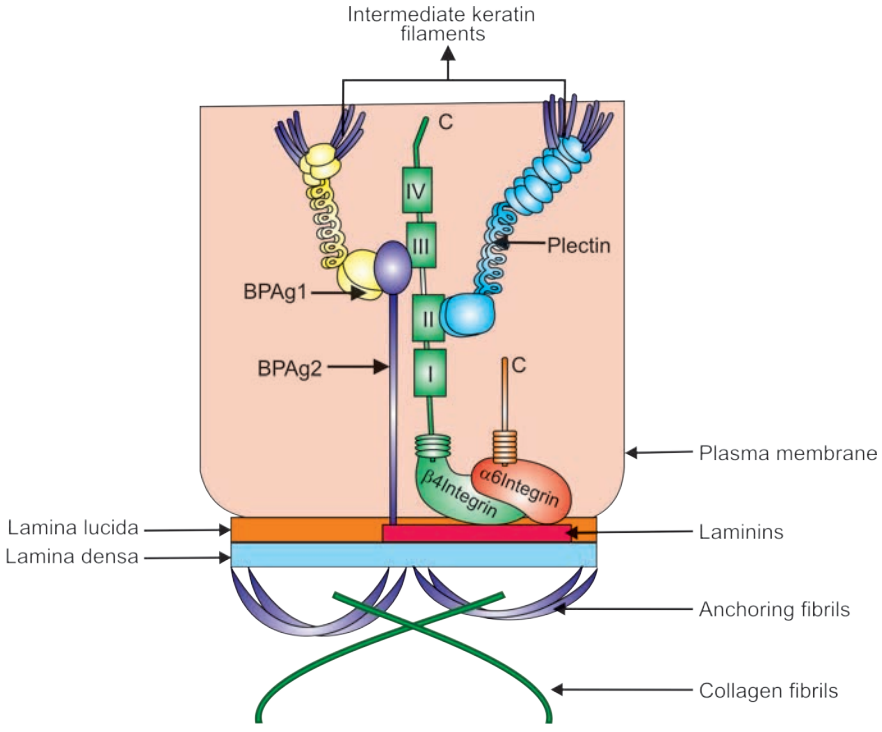

Fig. 9.4: Structure of hemidesmosome

connected to transmembrane proteins such as BPAg2 and α6β4 integrin. In the lamina lucida, these transmembranous proteins are linked to laminins, which in turn are linked to underlying lamina densa proteins such as type IV collagen or fibronectin. Finally, the lamina densa proteins are linked to type VII collagen anchoring fibrils.

Pathogenesis

Like pemphigus vulgaris, mucous membrane pemphigoid is also caused by a type II hypersensitivity reaction, but the target antigens are different. Autoantibodies (IgG or IgA or both) attack one or more antigen sites present in the basement membrane zone. The major antigens involved in MMP are believed to be BPAg2, and laminins. Consequently, the epithelium is poorly anchored to the underlying basal lamina and separates, allowing a subepithelial cleft to form. Circulating autoantibodies (IgG and IgA) against BPAg2 and laminins are usually found and the titer is generally correlated with severity of clinical disease.

Clinical Features

MMP is found in 2–5 people per 100,000 population a year and is seen more often in women. MMP most commonly develops during the 4^{th} to 7^{th} decade of life.

Clinical Presentation

MMP usually appears suddenly, is painful, waxes and wanes in severity and lasts for years or may be active throughout the remainder of the patients life. Oral lesions are not life threatening, but may be associated with considerable morbidity in patients who do not respond to medication. Since the hemidesmosome is the primary attachment mechanism between keratinocytes and the BMZ, the inflammatory destruction of hemidesmosome leads to the development of characteristic fluid filled bullae. The bullae quickly rupture, leaving a relatively nonspecific, shallow ulceration with an irregular border. Scarring from gingival lesions is not seen, but may occur in other oral areas, with associated reduced function. The ulcerations may affect other mucous membranes, including the conjunctiva, nasal mucosa, pharynx, larynx, esophagus and genital mucosa. The clinician must always rule out ocular and respiratory tract lesions.

Diagnosis

The definitive diagnosis of MMP cannot be based solely on clinical examination, as several other oral vesiculobullous lesions have a similar appearance (bullous lichen planus, pemphigus vulgaris and erythema multiforme). An incisional biopsy containing normal intact epithelium as well as tissue from the area of the ulceration is required for a definitive diagnosis. The characteristic histopathological features of MMP include subepithelial cleft due to detachment of the epithelium from the underlying basal lamina and dense mononuclear lymphocytic infiltration in the underlying connective tissue (Fig. 9.5). Direct immunofluorescence staining technique shows a linear deposit of IgG, IgA, C3, or a combination of these in the BMZ.

Treatment

Patients with involvement of the conjunctiva and pharyngeal, laryngeal, and genital mucosa should be referred to appropriate medical personnel for therapy. Patients who exhibit only mild oral lesions may require no treatment, as the risk of therapeutic side effects outweighs the benefit of the treatment. Many patients develop a tolerance to the oral lesions and cease complaining about oral discomfort despite the persistence of mild disease. The first line of treatment for those with only oral lesions is the

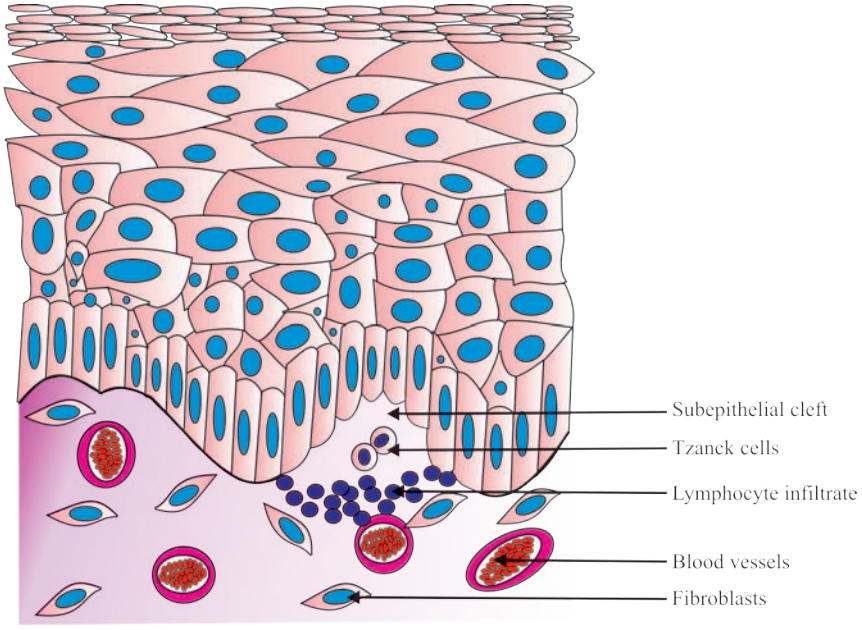

Fig. 9.5: Subepithelial cleft in mucous membrane pemphigoid

use of topical corticosteroids. However, this treatment often fails. Systemic corticosteroids, such as prednisolone, may achieve success in some patients. Cyclophosphamide, azathioprine, and methotrexate are used in combination with systemic corticosteroids. Patients resistant to corticosteroid therapy may benefit from dapsone (avlosulfone) therapy or combined tetracycline and nicotinamide therapy. Recently, topical tacrolimus has been used experimentally with some success on a patient with genital lesions. Intravenous immunoglobulin (IVIG) has been tried with some success. Patients who do not respond to any combination of treatments continue to suffer intensely for decades. In all cases involving the gingiva, excellent oral hygiene is recommended in order to reduce plaque, despite the presence of desquamative gingivitis.

HERPES VIRUS INFECTIONS

General Characteristics of Viruses

Viruses are infectious agents that are too small to be seen with a light microscope and that are not cells. They have no cell nucleus, organelles, or cytoplasm. Viruses differ from prokaryotic or eukaryotic cells in important ways. Individual virus particles contain only one kind of nucleic acid-either DNA or RNA but never both, unlike prokaryotic or eukaryotic cells, which contain both DNA and RNA.

Prokaryotic or eukaryotic cells grow and divide, but viruses do neither. Viruses can replicate, only inside a living host cell. Therefore, they are called obligate intracellular parasites.

Components of Viruses

The virus components are a nucleic acid core and a surrounding protein coat called a capsid. In

addition, some viruses have a surrounding lipid bilayer membrane called an envelope. A complete virus particle, including its envelope, is called a virion.

Host Range

The host range of a virus refers to the spectrum of hosts that a virus can infect. The host range of Rhabdoviridae (rabies) virus is very extensive. However, most viruses are limited to only one host and to only one specific cell of the host.

Specificity of Viruses

Viral specificity refers to the specific kind of cells or tissues a virus can infect. Therefore, viruses are grouped as dermotropic if they infect the skin, neurotropic if they infect the nervous system, viscerotropic if they infect the digestive system, pneumotropic if they infect the respiratory system and lymphotropic if they infect the lymphocytes.

Viral specificity is determined mainly by three factors:

1. ***Attachment:*** Attachment depends on the presence of specific receptors on the surfaces of host cells and specific attachment structures on viral capsids or envelopes.
2. ***Host enzymes:*** Specificity also depends whether appropriate host enzymes and other proteins the virus needs to replicate are available inside the cell.
3. ***Release:*** Finally, specificity is affected by whether replicated viruses can be released from the cell to spread the infection to other host cells.

Classification of Viruses

Viruses were first classified by the type of host they infected. Thus, viruses have been classified as bacterial viruses, plant viruses, and animal viruses.

As more was learned about the structure of viruses at the molecular level, the viruses were classified by the type of nucleic acid they contained.

As more viruses were discovered, conflictions in classification systems resulted. The need for a single, universal taxonomic scheme for viruses led to the establishment of the International Committee on Taxonomy of Viruses (ICTV) in 1996. This committee, which meets every four years, establishes the rules for classifying the viruses.

Herpes Viruses

The herpes viruses (*herpes*, Greek for "creeping") are relatively large, icosahedral, enveloped viruses with linear (double stranded DNA) dsDNA. The structure of the herpes virus is very complex (Fig. 9.6). The core consists of dsDNA. The capsid surrounds the core. Surrounding the capsid is the matrix or tegument, which contains at least 15-20 proteins. On the outside is the envelope, which contains at least eight glycoproteins. Herpes viruses are widely distributed in nature, and most animals are infected with one or more of the 100 types discovered. At least, seven distinct human herpes viruses have been described each causing a characteristic disease (Table 9.1). An important feature common to all the human herpes viruses

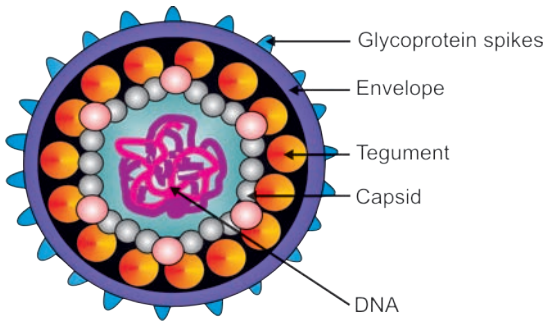

Fig. 9.6: Herpes simplex virus-1 structure

Table 9.1: Human herpes viruses

Genus	*Virus type*	*Disease*
Simplex virus	Herpes simplex virus type 1 Herpes simplex virus type 2	Oral herpes (sometimes genital) Genital herpes (sometimes oral)
Varicellovirus	Varicella-zoster virus	Chickenpox (Varicella); shingles (Herpes Zoster)
Cytomegalovirus	Cytomegalovirus (salivary gland inclusion virus) (human herpes virus 5)	Infectious mononucleosis; Acute febrile illness; Kaposi's sarcoma linked to AIDS; infections in transplant recipients; birth defects
Roselovirus	Roseola infantum (formerly called herpes virus 6)	Exanthema subitum (roseola infantum), a common disease seen in infants, featuring rash and fever
Lymphocryptovirus	Epstein-Barr virus (human herpes virus 4)	Infectious mononucleosis; Burkitt lymphoma; Hodgkin disease; B-cell lymphomas; nasopharyngeal cancer; Oral hairy leukoplakia linked to AIDS
Human herpes virus 8	Kaposi's sarcoma virus	Kaposi's sarcoma linked to AIDS

is their ability to establish latency in the host. Both herpes simplex virus type-1 (HSV-1) and herpes simplex virus type-2 (HSV-2) are res-ponsible for primary oral herpes simplex infections, with HSV-1 accounting for 75% to 90% of cases.

Replication of Herpes Simplex Virus

In general, viruses go through the following five steps in their replication cycle to produce virions.

1. Adsorption *(attachment of viruses to host cells)*
2. Penetration *(entry of genome into host cells)*
3. Synthesis *(synthesis of viral dsDNA and proteins)*
4. Maturation *(assembly of the viral components)*
5. Envelopment and release *(acquiring envelope and release of new virions from host cells)*

Adsorption

For the initiation of infection the HSV dsDNA must enter the host cell. The initial association is between proteoglycans of the host cell membrane and glycoprotein gC present on the viral envelope. This is followed by interaction between HVEM (herpes virus entry mediators) and glycoprotein gD present on the viral envelope. The HVEM are receptors for nerve growth factor and tumor necrosis factor present on the host cell membrane. Fusion of the viral and host cell membranes follows. This requires the action of a number of viral glycoprotein's including gB, gH, gI, and gL, which bind to corresponding receptors on the host cell membrane.

Penetration

Once inside the host cell, the viral capsid with some tegument proteins migrates to the nuclear pore along microtubules utilizing cell transport machinery. The viral dsDNA is then injected through the nuclear pore while the capsid remains in the cytoplasm. Some tegument proteins, such as αTIF, also enter the nucleus with the viral dsDNA.

Synthesis

There are two main events in the replication of herpes simplex virus, designated as early and late transcription. Early transcription is subdivided into two phases-immediate early and early. The early transcription takes place before the replication of dsDNA and results in the production of proteins necessary for viral dsDNA replication.

1. **Immediate-early phase:** In the immediate-early phase, α-mRNAs are transcribed, which translate α4-proteins in the cytoplasm.
2. **Early phase:** In the early phase, β-mRNAs are transcribed, which translate β-proteins in the cytoplasm.

These proteins (α4-proteins and β-proteins) migrate back to the nucleus, and mediate the replication of the viral dsDNA. The late events occur in the nucleus after the replication of dsDNA and result in transcription of structural mRNAs and transcription of new structural proteins needed for building new capsids.

The structural proteins migrate back to the nucleus (scaffolding proteins and procapsid proteins), inserted into nuclear membrane (viral glycoproteins), inserted into host cell membrane (viral glycoproteins), and float within the cytoplasm (αTIF and vhs tegument proteins).

Maturation

Once an abundance of dsDNA and structural proteins have been synthesized, they are assembled into new capsids. This step constitutes maturation. The scaffolding proteins (UL19, UL26 and UL26.5) assemble and form scaffolding. The procapsid proteins (UL18 and UL38) assemble around scaffolding following which the scaffolding proteins are digested away. The empty capsid incorporates viral dsDNA by means of the action of cleavage/packaging proteins. Vesicles transport viral glycoproteins that have been translated earlier (during synthesis) from structural mRNAs on the rough endoplasmic to the nuclear membrane. The mature capsid migrates to the nuclear membrane and buds into the lumen between the inner and outer nuclear membrane. This capsid then enters the cytoplasm as cytoplasmic capsid through fusion with the outer nuclear membrane.

Envelopment and Release

Viral glycoproteins that have been translated earlier (during synthesis) from structural mRNAs on the rough endoplasmic reticulum are transported to the Golgi body in vesicles, which are then transported in vesicles to modify the host cell membrane. The cytoplasmic capsid then associates itself with αTIF and vhs tegument proteins and buds into an exocytotic vesicle. The exocytotic vesicle migrates to virus modified cell membrane. Here it fuses with the virus modified cell membrane and acquires an envelope. The new virion is released outside the cell. Release of new virion results in lysis of keratinocytes.

CLINICAL MANIFESTATIONS

Primary HSV Infection

Primary HSV infections develop in people who have not been previously exposed to the virus. Transmission occurs *via* direct contact (thigmotaxis) with contaminated secretions from an infected individual. Mucosal surfaces and skin with cracks are highly susceptible. The most commonly observed clinical manifestation of primary HSV infection is primary acute herpetic gingivostomatitis (inflammation of gingiva and other intraoral mucosal surfaces). Primary acute herpetic gingivostomatitis is most often seen in children and adolescents. Most often, exposure to HSV infection in children results in a subclinical infection and the child may complain of mild flulike symptoms. Approximately 1% of patients develop primary herpetic gingivostomatitis. After an incubation period of 1 to 26 days, nonspecific signs and symptoms (prodromal) such as fever, malaise, irritability, headache, and cervical lymphadenopathy occur. The prodromal signs and symptoms are followed by eruption of vesicles. The vesicles affect any intraoral mucosal surface (buccal mucosa, hard/soft palate, floor of the mouth, tongue, gingiva, tonsillar pillars, and pharynx). The vesicles rupture within a few days to produce painful, small, round, shallow ulcers. Often, ulcers coalesce to form larger irregular-shaped ulcerations. Gradual healing, without scarring, occurs within 1 to 2 weeks.

Recurrent HSV Infection

Approximately 30 to 40% of patients who have been exposed to HSV will develop recurrent HSV infections. Recurrent HSV infections can either occur as recurrent herpes labialis (RHL) or recurrent intraoral herpes (RIH). These recurrent HSV infections represent reactivation and not reinfection of HSV. During primary HSV infection, the virus is transported *via* retrograde axonal transport to regional sensory ganglia where it establishes latency in nerve cell bodies (Fig. 9.7). While latent, the virus exists in a nonreplicating immunologically shielded state. The most frequent site of latency for HSV is the trigeminal ganglion, but other potential sites include the nodosa ganglia of the vagus nerve, dorsal root ganglia, sympathetic ganglia, and brain. Numerous well-documented triggering factors are associated with HSV recurrence. They include sunlight, trauma, menstruation, fever, immunosuppression, decompression of the trigeminal nerve, and irritation by dental instruments. Once, reactivated the virus is transported *via* anterograde transport to the epithelium where it replicates, causing tissue damage and recurrent HSV infection. The limited virus replication takes place until the host defense systems respond and suppress it. It is not known whether the reactivation involves the killing of one or more neurons, but evidence suggests that the frequency of reactivation decreases with time.

Recurrent Herpes Labialis

Recurrent herpes labialis is the most predominant recurrent HSV infection. Prior to RHL patients experience prodromal signs and symptoms such as burning, tingling, itching, soreness or swelling at the site where the lesions will develop. Within hours, small vesicles develop along the vermilion border of the lips and other perioral sites such as the skin or ala of the nose. The characteristic clinical appearance of RHL is focal clustering of vesicles (Fig. 9.8). The vesicles quickly rupture, resulting in ulcers that coalesce to form the larger irregular-shaped ulcers with a crusted surface (Figs. 9.9 A and B). In a healthy individual, the lesions heal without scarring within 7 to 14 days.

Recurrent Intraoral Herpes

RIH lesions occur less frequently than RHL. RIH lesions begin as clusters of tiny vesicles that rupture quickly, resulting in erosions or ulcers without crusting. The RIH lesions involve

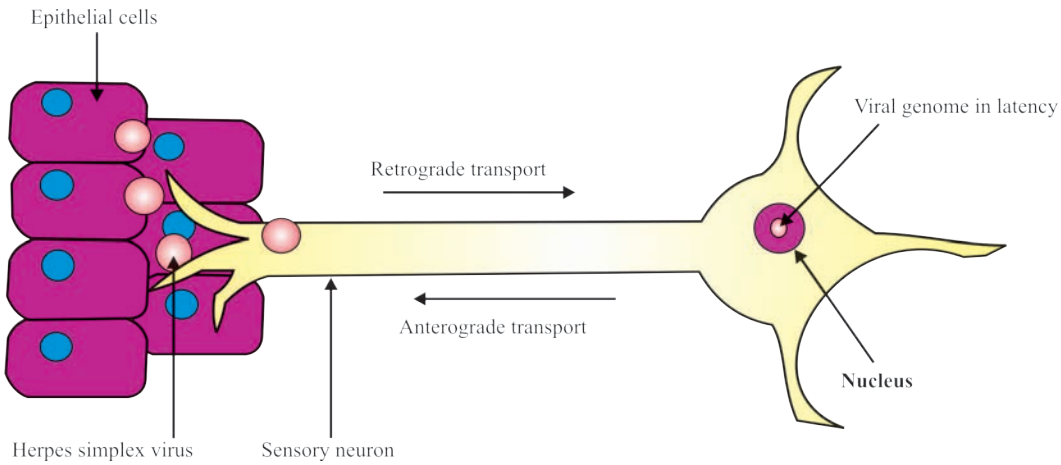

Fig. 9.7: Herpes simplex virus-1 latency

Fig. 9.8: Focal clustering of vesicles

Figs 9.9A and B: Recurrent herpes labialis with crusted surface

keratinized mucosa (hard palate, attached gingiva, and edentulous ridges) (Fig. 9.10). However, in immunocompromised patients e.g., AIDS, the tongue can also be affected. The lesions on the tongue exhibit mucosal erosions, each of which is surrounded by a circinate, raised, yellow border (Fig. 9.11). This border represents the advancing margin of active viral destruction. Intraoral recurrence follows a pattern of presentation similar to that of RHL except the lesions are intraoral, and crusting does not occur. The pain associated with RIH may interfere with eating and speaking. In a healthy individual, the lesions heal without scarring within 7 to 14 days.

Fig. 9.10: Recurrent intraoral herpes

Fig. 9.11: HIV-associated recurrent intraoral herpes

Recurrent herpetiform aphthous ulcers and RIH have similar clinical presentation except the recurrent herpetiform aphthous ulcers are seen anywhere on the oral mucosa and patients do not experience prodromal signs and symptoms.

Differential Diagnosis

The diagnosis of RHL is based on their characteristic clinical appearance of the lesions. However, the diagnosis of RIH is based on the clinical appearance of the lesions and their location. However, other oral mucocutaneous diseases should be considered in the differential diagnosis (Table 9.2)

Table 9.2: Differential diagnosis of oral HSV infection

Differential diagnosis	*Clinical appearance*
ANUG	Fiery red gingiva, interproximal crater formation
Erythema multiformae	Oral ulcerations, target lesions on skin
Hand-foot-and-mouth disease	Multiple aphthouslike ulcerations and lesions on hand and feet
Herpangina	Bandlike oral ulcerations affecting soft palate, uvula, tonsils, and posterior pharyngeal wall
Intraoral shingles	Oral ulcerations, skin lesions, severe pain
Pemphigus vulgaris	Oral ulcerations, positive Nikolsky's sign
Recurrent herpetiform aphthous ulcers	Recurrent, clustered, small, shallow intraoral ulcers affecting any part of oral mucosa, no prodrome of fever and malaise

Diagnosis

Tzanck Test (Mucosal Smear)

The Tzanck test is a rapid and inexpensive diagnostic aid useful in the diagnosis of HSV infection. A sterile scalpel is used to unroof a vesicle, and the base of the vesicle is gently scrapped on a glass slide. The scrapping is allowed to dry in the air for couple of minutes and then stained with Wright Giemsa stain for microscopic examination. Characteristic multinucleated epithelial cells with intranuclear inclusions indicate a positive test.

Other diagnostic tests include tissue biopsy, viral culture, serology, and polymerase chain reaction, but are not routinely used.

Dental Care

The vesicular stage of recurrent HSV infection is the most contagious. However, all stages of recurrent HSV infections are infectious until complete re-epithelialization has occurred. Patients must be informed that recurrent HSV infections are extremely contagious and therefore care must be taken to avoid autoinoculation of other mucosal sites, as well as transmission to others.

Health care workers are highly susceptible to herpetic infection of the finger known as herpetic whitlow (herpetic paronychia). Paronychia is the infection in the tissues adjacent to a nail on a finger or toe. Herpetic whitlow often occurs as a result of failure to use gloves when the hand is in contact with the infected secretions such as saliva because HSV is sloughed asymptomatically in the saliva of patients during healing of RIH.

Signs and symptoms of herpetic whitlow include sudden onset of edema, erythema, intense itching, and localized tenderness of the infected finger. This is followed by eruption of vesicles and formation of pustules and is usually accompanied by fever and lymphadenopathy (axillary lymph nodes). The vesicles and pustules eventually rupture to become ulcers. The duration of herpetic whitlow may be as long as 4 to 6 weeks. Recurrences may also occur with this form of herpes infection and usually involve the same site. Recurrent lesions may result in paresthesia and permanent scarring.

To summarize health care workers should use gloves, face masks, and protective spectacles if the patient infected with HSV is to be treated. Because transmission occurs *via* direct contact with contaminated saliva from an infected individual, care must be taken not to spread the virus to the finger and other mucous membranes, such as eyes or nasal mucosa. For this reason, air-water sprays should be avoided unless a rubber dam is used. Trauma to the lesion must be avoided so that healing will not be retarded.

Management

Therapy for HSV infection is dependent on the clinician's evaluation of both the clinical presentation and patients overall health. For example, the management of RHL affecting a healthy patient will differ from the management of RHL affecting an AIDS patient. Treatment of HSV infection is symptomatic and has four major goals:

1. Ulcer management (to promote healing and reduce duration)
2. Pain management (to reduce morbidity *(the relative incidence of a particular disease)* and to enhance function)
3. Nutritional management (to ensure adequate food and fluid intake)
4. Disease control (to prevent recurrence or reduce frequency)

Primary HSV Infection

The treatment of mild cases of primary herpetic gingivostomatitis is directed at relieving discomfort and improving the patients ability to eat and drink. The patient is instructed to maintain adequate food and fluid intake, and maintain proper oral hygiene. A topical anesthetic agent is prescribed which is to be used for 2 minutes before each meal. Non-steroidal anti-inflammatory drugs can also be prescribed to relieve fever and pain.

Antiviral therapy for the immunocompromised patient should include systemic antiviral therapy. Systemic acyclovir therapy, both parenteral and oral, accelerates viral shedding, reduces pain, and reduces healing time. For intravenous administration, the regimen is 5 mg/kg (infused over 1 hour) every 8 hours for 5 to 10 days. A generally accepted oral regimen is 400 mg taken 3 to 5 times per day for 10 days.

Acyclovir is a synthetic analogue of purine guanosine that inhibits viral DNA polymerase and thereby inhibits viral dsDNA replication. Acylovir is active only in virally infected cells because only viral-encoded enzyme thymidine kinase converts acyclovir to acyclovir monophosphate. Cellular enzymes (cellular kinase) then phosphorylate acyclovir monophosphate to acyclovir triphosphate, which is the active form of the drug. Failure of acyclovir therapy is usually associated with HSV infections caused by thymidine kinase-deficient strains of HSV. It should be noted that these drugs such as acyclovir act against the replicating virus and therefore they are ineffective against latent virus.

Foscarnet therapy should be initiated in immunocompromised patients who fail to improve with acyclovir therapy. Foscarnet does not require activation *via* phosphorylation by viral thymidine kinase. Foscarnet is also active against HSV-1, HSV-2, VZV, cytomegalovirus (CMV), influenza A and B, hepatitis B virus (HBV), and HIV. Foscarnet causes renal failure and therefore adequate hydration is critical, as is proper monitoring and dose adjustment to minimize toxicity. Therapy consists of intravenous foscarnet 40 mg/kg every 8 to 12 hours for 14 to 21 days.

Recurrent HSV Infection

The treatment of RHL is primarily symptomatic as in primary herpetic gingivostomatitis. Topical antiviral ointments can be used as they accelerate

viral shedding, reduce pain, and reduce healing time. Topical acyclovir 5% ointment applied during prodromal symptoms to the affected area every 2 hours 6 times per day for 7 days until resolution may be sufficient to control RHL. Topical penciclovir (1%) ointment applied during prodromal symptoms to the affected area every 2 hours while awake for 4 days has been shown to speed lesion healing and reduce pain. Recently, docosanol (10%) ointment became available for the treatment of RHL. The mechanism of action of docosanol is *via* alteration of healthy cell membranes to prevent viral entry. Docosanol ointment applied during prodromal symptoms to the affected area 5 times per day for 4 days may be sufficient to control RHL. Because sunlight is a known triggering factor of RHL, prevention may be enhanced by using a sunscreen lotion with a sun protection factor (SPF) 15 or greater.

However, immunocompromised patients fail to improve with topical antiviral therapy. In such patients oral famciclovir is indicated. The recommended dosage is 500 mg twice daily for 7 days, initiated at prodrome. In addition, the use of oral acyclovir has been shown to be effective. For episodic therapy, the prompt (at the first prodromal symptom) administration of oral acyclovir, 400 mg 3 times per day for 10 days, may be sufficient. For patients who have frequent recurrences (more than six episodes per year), chronic suppressive therapy with oral acyclovir, 400 mg 2 times per day, may prevent recurrence. Foscarnet therapy should be initiated in immunocompromised patients who fail to improve with acyclovir therapy.

Shingles

Shingles of the trigeminal nerve is a disease that falls within the diagnostic purview of all dentists and dental specialists. During the prodromal stage of this disease, the only presenting symptom may be odontalgia. This odontalgia is a diagnostic challenge to the clinician who is not familiar with shingles of the trigeminal nerve.

Varicella-zoster Virus

The varicella-zoster virus is responsible for two common infectious diseases:

1. **Primary infection**—chickenpox
2. **Secondary infection**—shingles

After the primary infection, the virus remains dormant until there is reactivation that may occur decades later. The subsequent reactivation is shingles (Fig. 9.12)

Reactivation

Numerous well-documented triggering factors are associated with reactivation of VZV. They include neonates, nonimmune persons, pregnant women, and immunocompromised patients.

Transmission

Chickenpox and shingles are contagious and spread *via* direct contact with an infected person. The transmission can also occur through inhalation of airborne respiratory secretions. The virus then infects the cells of the respiratory tract or conjunctival epithelium and is transported

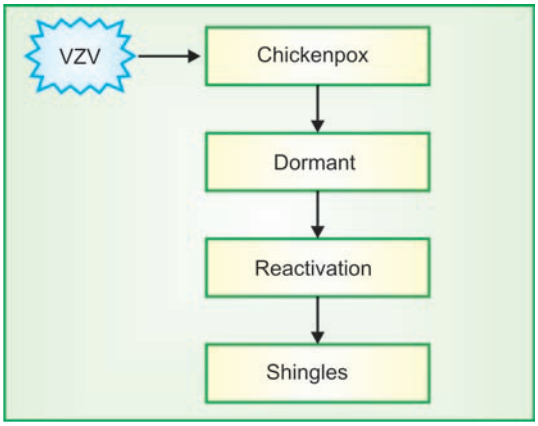

Fig. 9.12: Reactivation of varicella-zoster virus

through the body *via* blood and lymphatic system. The virus then spreads from the capillaries to the epidermis where it replicates and destroys the basal cells. Following which the virus migrates to the primary satellite cells of the dorsal nerve root ganglia, where it establishes latency in the nerve cell bodies (Fig. 9.13).

Shingles

Shingles may affect any sensory ganglia and its cutaneous nerve. Most of the infections affect dermatomes of T-3 to L-2 (Fig. 9.14). However, in 13% of patients it involves any three branches of the trigeminal nerve (Fig. 9.15). Ocular branch (V_1) involvement is the most common trigeminal nerve infection (50% of all trigeminal occurrences). Hutchins' sign is pathognomonic, when shingles involves the maxillary branch. Hutchins' sign is characterized by cutaneous lesions of one side of the tip of the nose.

Diagnostic Stages

Patients with shingles usually progress through three diagnostic stages (Fig. 9.16):

1. Prodromal stage
2. Active or acute stage
3. Chronic stage

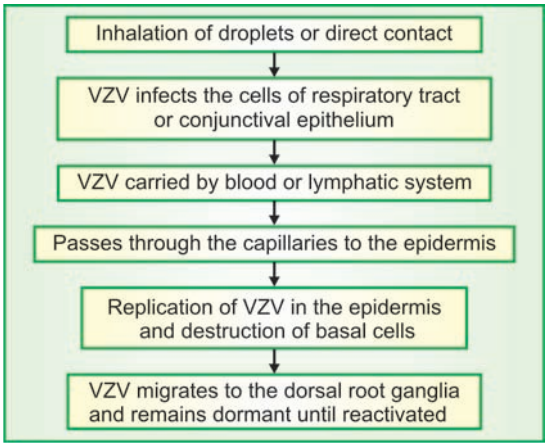

Fig. 9.13: Transmission of varicella-zoster virus

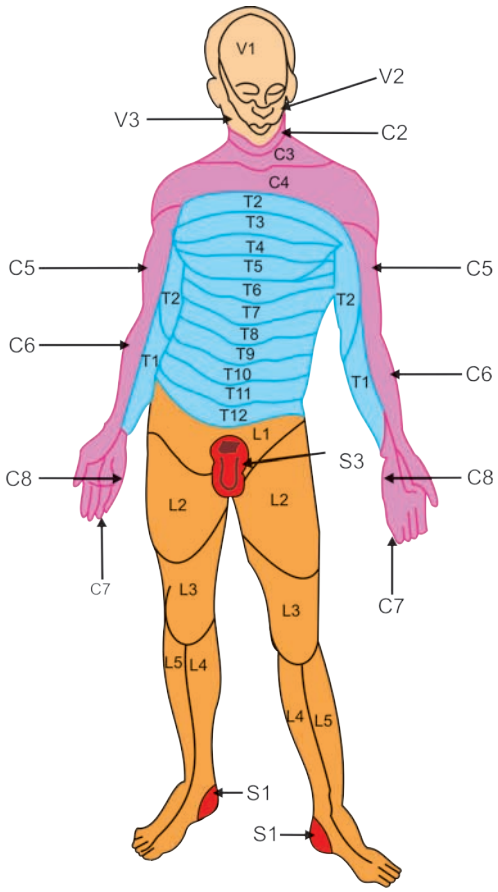

Fig. 9.14: Dermatomes

Fig. 9.15: Herpes-zoster involving mandibular nerve

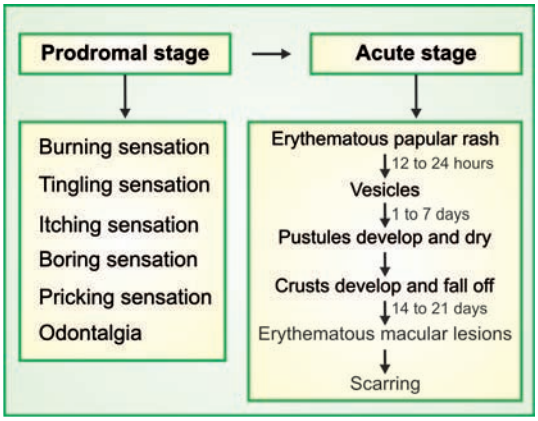

Fig. 9.16: Diagnostic stages

Fig. 9.17: Perioral vesicles

Fig. 9.18: Intraoral lesions

Prodromal Stage

The prodromal stage presents with different types of sensations occuring in the skin over the affected nerve distribution they include.

1. Burning
2. Tingling
3. Itching
4. Boring
5. Prickly or knife-like

It is believed that these sensory changes are due to degeneration of nerve fibrils because of viral infection. The sensory changes usually precede (come before) the rash of the acute stage. The patient may present with odontalgia, which may be the only prodromal symptom.

Acute Stage

The active stage is characterized by the emergence of rash, which may be accompanied by generalized malaise, headache, low-grade fever, and sometimes nausea. The rash progresses from erythematous papules to vesicles in 12 to 24 hours (Fig. 9.17). The vesicles progress to pustules within 1 to 7 days. The pustules begin to dry and form crusts. These crusts fall off within 14 to 21 days, leaving erythematous macular lesions, which result in hyperpigmented or hypopigmented scarring. In severe cases, areas of epidermis and dermis may be lost. Intraoral lesions usually appear after the cutaneous rash (Fig. 9.18). Pain and dysaesthesia are minimal when the rash is active. However, the pain returns during crust formation, but subsides as the crusts clear off.

Chronic Stage

The chronic stage is termed postherpetic neuralgia (PHN). PHN is pain lasting for 1 to 3 months after the skin lesions disappear but may in fact last for years and decades. PHN pain consists of three distinct components:

1. Constant, deep pain
2. Brief recurrent shooting or shocking tic-like pain

3. Sharp radiating dysaesthetic sensation evoked by very light touching of the skin

Differential Diagnosis

The dental practitioner should be familiar with various diseases that can produce facial pain. The diagnosis of shingles is clear when the prodromal symptoms and the rash are present. A diagnostic challenge is created when the vesicular rash does not occur, as in *zoster sine herpete* (Herpes zoster without rash) of the trigeminal nerve and a culture may be required to confirm shingles. A detailed and careful case history usually rules out other pathologies such as:

1. Trigeminal neuralgia
2. Maxillary sinusitis
3. Periodic migrainous neuralgia
4. Myocardial pain
5. Atypical facial pain
6. Munchausen's syndrome

Complications

The clinical presentations of shingles are variable and extend beyond the region of head and neck. The complications can range from meningoencephalitis to superficial skin changes. It is important to remember that any part of CNS can be affected.

Neurological Complications

1. Meningoencephalitis
2. Horner's syndrome
3. Ramsey-Hunt syndrome
4. Guillian-Barre syndrome

Ocular Complications

1. Ulcerations
2. Hemorrhage
3. Conjunctivitis
4. Optic neuritis

Dental Complications

1. Tooth neuralgia
2. Devitalization of teeth
3. Internal root resorption
4. Tooth exfoliation and osteonecrosis of mandible *(upon resolution of acute phase).*
5. The contralateral side of the patient's jaw remains normal.

Miscellaneous Complications of Various Organs

1. Skin
2. Heart
3. Liver
4. Joints of the musculoskeletal system
5. Urinary tract

Management

The recommended therapy for shingles should include:

1. Patient isolation
2. Management of skin lesions
3. Control and elimination of pain
4. Antiviral drugs
5. Management of PHN pain

Patient Isolation

Patients with shingles are contagious to persons at high risk. They include neonates, nonimmune persons, pregnant women, and immunocompromised patients. Patients with shingles remain contagious until crusting phase has taken place.

Management of Skin Lesions

Management of skin lesions includes, soaking of gauze is in cool water and applying to the rash area for 30 minutes 3 to 6 times a day. Creams and lotions may be used after the acute phase to soften and remove adherent crusts. Creams and lotions containing corticosteroids are not recommended.

Control and Elimination of Pain

The acute pain of shingles during the prodromal and the acute phases can be reduced. Mild to moderately strong analgesics, such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAID) are effective.

Antiviral Drugs

Once shingles is diagnosed, antiviral therapy must be swift and precise. Acylovir has been the drug of choice for a number of years for many reasons. Recently newer forms of antiviral drugs have been developed specifically to manage acute stage of shingles (famciclovir) and for use in immunocompromised patients (valacyclovir).

Antiviral drugs may help in limitation of the extent, duration, and severity of the disease. Acylovir has been proven to decrease drastically the duration and severity of shingles in the acute phase, if administered within 48 hours of the onset of rash. Acylovir is less toxic than other antiviral drugs. The dosages of various antiviral drugs used in the management of shingles are listed in the Figure 9.19.

Management of PHN Pain

Standard NSAID are not effective in patients with PHN pain. The PHN pain is because of injury to the CNS and therefore is unlikely to respond to standard NSAID. The treatment of PHN pain is varied. However, no single treatment is universally effective for all PHN patients. The various treatment modalities of PHN include.

1. Topical use of capsaicin cream (Capsain-P gel, 25 gm, which contains capsaicin 0.025 w/w)
2. Transcutaneous electric nerve stimulation (TENS)
3. Topical anesthetics
4. Injected local anesthetics
5. Low dose tricyclic antidepressants such as amitriptyline, 10-25 mg 3 times a day, till desired results are achieved

Antiviral drug	Dosage
Acylovir	800 mg four-five times a day for 10 days remains the standard
Famciclovir	500 mg every 8 hours for 7 days
Valacyclovir	1 gm three times daily for 7 days

Fig. 9.19: Antiviral drugs and dosages

ORAL LICHEN PLANUS

Lichen planus is a common mucocutaneous disease, which was first described by Erasmus Wilson in 1869. The condition can affect either the skin or mucosa or both. Cutaneous lesions typically present as small (2 mm) pruritic, white to violaceous papules, which can increase in size to 3 cm. They often occur bilaterally on the flexor surfaces of the extremities.

Oral lichen planus is a chronic disease that can persist in some patients for a long time in contrast to cutaneous lichen planus. It often does not respond to treatment and complete remissions are rare, particularly in patients with erosive lesions. Exacerbations are unpredictable and common. There is no cure and the treatment is symptomatic.

Clinical Features

Oral lichen planus is a disease of adulthood and children are rarely affected. It affects woman more often than men and is usually observed in nervous, "highly-strung" people.

Oral lichen planus may present anywhere in the oral cavity. The buccal mucosa, tongue and

gingiva are the most common sites, whereas palatal lesions are uncommon. They are usually symmetrical and bilateral lesions (mirror-image lesions).

Clinical Variants

Oral lichen planus is divided into six types: reticular, papular, plaquelike, erosive, atrophic and bullous. The reticular, papular and plaque-like forms are usually painless and appear clinically as white keratotic lesions. The erosive, atrophic and bullous forms are often associated with burning sensation and in many cases can cause severe pain.

Reticular

The most common type of oral lichen planus is the reticular form. Characteristically, it presents as a series of fine, radiant, white striae known as "Wickham striae" (Fig. 9.20). The buccal mucosa is the most common site. The striae are typically bilateral and symmetrical. They may also be seen on the lateral border of the tongue and less often on the gingiva and the lips.

Fig. 9.20: Reticular lichen planus

Papular

The papular type of oral lichen planus presents as small white pinpoint papules measuring about 0.5 mm in size (Fig. 9.21). The buccal mucosa is the most common site. It is rarely seen and because the lesions are small it is possible to overlook them during a routine oral examination.

Fig. 9.21: Papular lichen planus

Plaquelike

The plaquelike type of oral lichen planus resemble oral leukoplakia and occur as homogeneous white patches. The dorsum of the tongue and the buccal mucosa are the most common sites. This form is much more common among tobacco smokers.

Erosive

The erosive type of oral lichen planus is the second most common type. The lesions are usually irregular in shape and covered with a pseudomembrane (Fig. 9.22). The periphery of the lesion is usually surrounded by fine, radiant, white striae. The buccal mucosa is the most common site. Gingival involvement in erosive lichen planus produces chronic desquamative gingivitis. Only the atrophic and erosive forms of lichen planus undergo malignant change (Fig. 9.23), and this may be because of the atrophic nature of the oral mucosa.

Atrophic

The atrophic type of oral lichen planus presents as diffuse, red lesion. The periphery of the lesion is usually surrounded by fine, radiant, white

Fig. 9.22: Erosive lichen planus

Fig. 9.23: Malignant change in erosive lichen planus

striae. The attached gingiva is often involved and the condition is commonly referred to as chronic desquamative gingivitis.

Bullous

The bullous type of oral lichen planus is rarer than the other forms of oral lichen planus and appears as vesicles or bullae that tend to rupture easily and form ulcers. The bullous form is commonly seen on the buccal mucosa, particularly adjacent to the second and third molar teeth. The next most common site is the lateral margins of the tongue. The lesions are rarely seen on the gingiva or inner aspect of the lips.

Oral Lichen Planus and Pigmentation

The appearance of hyperpigmentation in cutaneous lichen planus indicates the resolution of the lesion. Hyperpigmentaion in cutaneous lesions may result from melanin loss into the dermis from the damaged basal cell layer. However, no such conclusions can be made in regard to oral lichen planus.

Etiopathogenesis

The cause of oral lichen planus remains unclear. However, it is well-documented that oral lichen planus represents a chronic, cell-mediated autoimmune disease process with the infiltrating cell population composed of both CD4+ Tcells and CD8+ T cells targeted against basal keratinocytes of the oral mucosa in susceptible individuals.

Whether this chronic, cell-mediated auto-immune disease process progresses to the development of oral lichen planus, or is switched off, probably depends on a number of factors, which include:

1. The nature of the antigen
2. The ability of the individual to present the antigen
3. The presence of T cells capable of recognizing the antigen
4. Genetic susceptibility in the individual that promotes, rather than suppress, a cell-mediated autoimmune disease response to the antigen

Lymphocyte trafficking to the basal lamina – basal keratinocyte interface is the hallmark of oral lichen planus. No specific oral lichen planus antigen has been detected but it seems that various antigens are capable of inducing changes in the skin or oral mucosa. Some of the antigens known to induce changes are:

a. Dental restorative materials
b. Cinnamon-flavoring agents used in foods

c. Medications (medications are known to induce oral lichenoid lesions that can be difficult to distinguish from oral lichen planus)
d. Microbes

Peripheral immature dendritic cells IDCs e.g., Langerhans cells bind to the basal keratinocytes by expressing surface molecules such as E-cadherin. The principle function of IDCs is to pick up the antigen, and process it. After processing the antigen, under the influence of tumor necrosis factor α (TNF-α), produced by surrounding basal keratinocytes or the inflammatory infiltrate, these immature IDCs loose their E-cadherin and produce collagenase, in order to facilitate their crossing through the basement membrane.

They then travel as "veiled cells" via the afferent lymphatics to the paracortical T cell zone of the draining lymph node. In the paracortical T cell zone the immature IDCs become mature and interdigitate with the naive or virgin T cells and present the antigen with the help of MHC class II molecules and costimulatory molecules such as B7 (Fig. 9.24). The naive T cells once primed with the antigen become activated T cells, which undergo clonal proliferation and maturation (Fig. 9.25).

The basal keratinocytes produce chemotactic agents such as interleukin-1, interleukin-8, interleukin-10, and leukotriene-B, and transforming growth factor β. Production of these chemotactic agents from the basal keratinocytes results in infiltration of T cells from the underlying blood vessels to the basal lamina-basal keratinocyte interface.

This infiltration requires activation of integrins such as lymphocyte function associated antigen

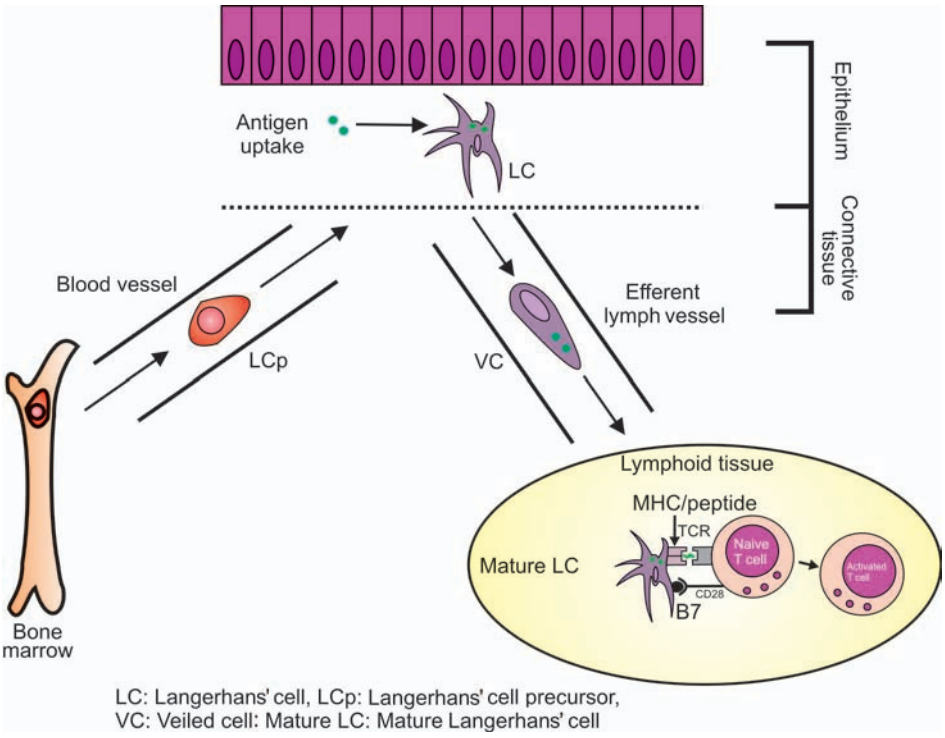

Fig. 9.24: Migration pathway of Langerhans' cell

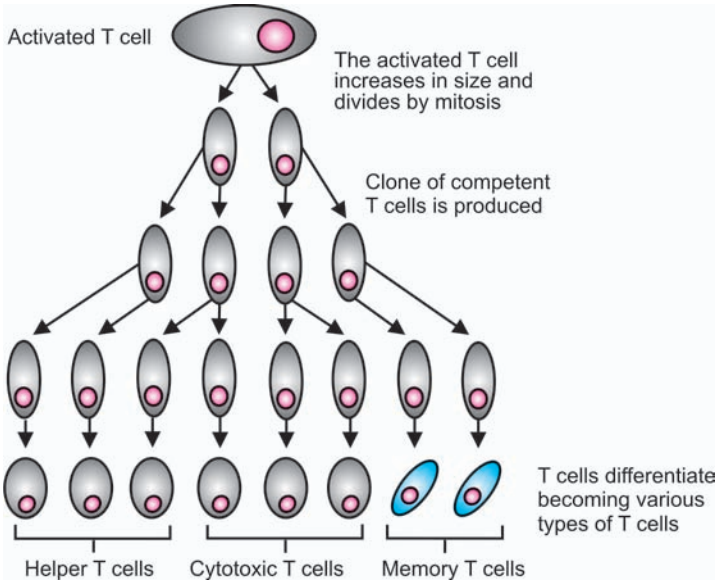

Fig. 9.25: Clonal proliferation of T cells

(LFA-1) on the plasma membrane of T cells. Integrins are normally expressed on T cell plasma membranes but do not adhere to their appropriate ligands until the T cells are activated by chemotactic agents.

Upon activation the T cell integrins adhere to their ligands (ICAM-1) and migrate towards the basal lamina-basal keratinocyte interface, which is likely to be under the control of chemotactic agents produced by the basal keratinocytes.

TNF-α and IFN-γ produced by the infiltrating T cells, induce the expression of adhesion molecules such as ICAM-1 (intercellular adhesion molecule) present on the lining of blood vessels in the affected oral mucosa.

The activated T cells produce IFN-γ, which induces keratinocytes to express antigen with the help of MHC class II molecules, increase their rate of differentiation (which results in thickening of the epithelium and is clinically seen as white lesion), and expression of intercellular adhesion molecule (ICAM-1) to which the activated T cells adhere. In addition, these same T cells express ICAM-1 and thereby allow lymphocyte to lymphocyte clustering.

Because both CD4+ T cell and CD8+ T cell are present in oral lichen plans lesions, it has been speculated that CD8+ T cell may be responsible for the apoptosis of basal keratinocytes layer, particularly in erosive, atrophic and bullous lichen planus.

There are two main mechanisms by which CD8+ T cell induce apoptosis in target cells such as basal keratinocytes. Both require intimate contact between the CD8+ T cell and the basal keratinocyte.

1. The first mechanism by which CD8+ T cell kill basal keratinocytes involves cross-linking of the cell surface molecule Fas on the basal keratinocyte by its ligand Fas-L expressed by CD8+ T cell and NK cells. This triggers a cascade of intracellular enzymatic reactions resulting in apoptosis of the target cell.
2. In the second mechanism, the CD8+ T cell produces the molecule perforin that polymerizes in the basal keratinocyte cell membrane to form holes through which the CD8+ T cell secretes the enzyme granzyme B that initiates the breakdown of intracellular proteins.

TNF-α produced by CD8+ T cell may also promote apoptosis in oral lichen planus. It induces differentiation and activation of CD8+ T cell, and NK cells. It is also anti-proliferative to basal keratinocytes and cytotoxic to them at high concentrations. Moreover, when produced directly onto the surface of basal keratinocytes by adherent CD8+ T cell, it may directly induce apoptosis or further enhance Fas/Fas-L mediated apoptosis.

Histopathology

The histopathological features were first described by Dubreuill in 1906 and later by Shklar. Shklar described the three classic microscopic features of oral lichen planus as overlying keratinization (hyperparakeratosis or hyperorthokeratosis), a band like layer of chronic inflammatory cells (T cells) within the underlying connective tissue and liquefaction degeneration of the basal keratinocytes. The other features include acanthosis, thickening of the granular cell layer, separation of epithelium from the underlying connective tissue due to basal cell destruction (typically seen in erosive forms), and blunted rete ridges. Intimate comingling of basal cells and T cells obliterates the epithelial-stromal interface and results in loss of definition of the stratum basale. In turn, this yields the jagged "candle dripping" or "saw tooth" appearance of rete ridges. In cutaneous lichen planus the rete ridges have a jagged "candle dripping" or "saw tooth" appearance. Colloid bodies (also termed cytoid, globular, hyaline, Civatte, and Sabouraud's bodies) may be seen lying either in the lower layers of the epithelium or within the upper layers of the connective tissue. They are round, eosinophilic globules and are probably degenerated epithelial cells or phagocytosed epithelial cell remnants within macrophages. Direct immunofluorescence studies show that these bodies stain for IgA, IgG and IgM. These histological features suggest a cell-mediated immune response.

Treatment

Many patients with oral lichen planus have no symptoms. In such cases, no active treatment is required except for reassurance. Most cases of asymptomatic lichen planus are detected during a routine check up. Patients who are not given any active treatment are advised to revisit every six months for two years, or earlier if they get symptoms.

Corticosteroids

The backbone of oral lichen planus treatment remains corticosteroids, which can be used topically, intralesionally or systemically.

Topical Corticosteroids

Topical corticosteroids may be used when systemic corticosteroids are contraindicated or if the patient refuses intralesional injections. Topical corticosteroids appear to be safe when applied to mucous membranes but prolonged use requires careful frequent follow-up. Topical betamethasone disodium phosphate applied orally may cause adrenal suppression and betamethasone valerate aerosol can be harmful or fatal when applied to mucous membranes. In addition, topical corticosteroids may result in the development of secondary oral candidosis. Therefore, adjunctive antifungal preparation should be considered. Triamcinolone acetonide ointment twice a day for two weeks and once a day for a further two weeks can be effective. Alternative treatment is required for patients whose symptoms do not respond to topical treatment.

Intralesional Corticosteroids

Intralesional injection of corticosteroids can improve the symptoms. A 5% mixture in local anesthetic has been recommended to lessen the

pain of the injections. Atrophy of tissue and secondary oral candidosis are possible local complications. It is difficult to inject sufficient quantities into gingival lesions. Intralesional triamcinolone acetonide 10 mg/ml repeated once or twice a week appear to be a practical supplement for the treatment of erosive-ulcerative lesions.

Systemic Corticosteroids

Systemic corticosteroids should be reserved for acute exacerbations of symptoms, multiple ulcerations, or widespread disease. Systemic corticosteroids are often used in combination with topical corticosteroids. Prednisolone 30-60 mg, depending on the severity of the disease, are given once daily for two to three weeks. Adverse effects are common even after a course as short as two weeks. The most common adverse effects include gastrointestinal upset, mood alteration, polyuria, and insomnia. Patients who take systemic corticosteroids should be monitored regularly.

Griseofulvin

Griseofulvin is indicated for the treatment of erosive-ulcerative lesions when corticosteroid treatment is contraindicated or when lesions are resistant to corticosteroids. When it is given orally or parenterally, it is distributed throughout the body and deposited in basal cells and progressively reaches the stratum corneum as the cells mature. The mechanism of action is not known. However, it is thought that it may prevent desquamation of the stratum corneum, and thereby prevent erosions.

Cyclosporin

Damage to the basement membrane in oral lichen planus is due to the production of lymphokines by CD8+ T cell. Cyclosporin is an immunosuppressant and inhibits the proliferation, function and production of lymphokines. Adverse effects of cyclosporin include renal dysfunction due to prolonged use, and transient burning sensation on the mucosal surface of the lesion. Treatment of oral lichen planus by cyclosporin is expensive so its use could be limited by cost.

Retinoids

Topical application of retinoids to asymptomatic, white, reticulated oral lichen planus has given good results. The most readily available topical retinoid is 0.1% tretinoin. But it may cause irritation and burning and lesions may relapse when it is withdrawn. The use of systemic retinoids such as etretinate is limited because of their adverse effects including dry skin and hair loss.

Dapsone

Dapsone should be considered in resistant cases, particularly in erosive-ulcerative lesions.

Photochemotherapy

Topical and systemic psoralen (8-methoxy-psoralen) and long-wave ultraviolet-A (PUVA) is a common treatment for various dermatoses. PUVA without topical and systemic psoralen is also effective. One drawback of PUVA is the possible development of squamous cell carcinoma, particularly as oral lichen planus is regarded as a premalignant condition. As of now these treatments should be considered experimental.

Surgery

Cryosurgery and carbon dioxide laser ablation have been suggested for the surgical treatment of plaque-like oral lichen planus. However, surgical excision is contraindicated in erosive and atrophic lesions as oral lichen planus is a chronic inflammatory condition that will recur.

Moreover, operative trauma to the oral mucosa may induce the formation of new lesions at these sites.

Oral Lichenoid Lesions

The appearance of lesions having the clinical and histopathological features of oral lichen planus, but apparently induced by drugs, has been recognized for some time but the importance was emphasized by the large number of cases of oral lichenoid lesions that appeared in service personnel receiving antimalarials in World War II.

Oral lichenoid lesions (Fig. 9.26) may be triggered by mechanical trauma (Koebner phenomenon) from calculus and plaque deposits, friction from sharp cusps, rough dental restorations, poorly fitting dental prostheses, tongue biting, lip biting or cheek biting (morsicatio buccarum), and oral surgical procedures. When these factors are removed or eliminated the lesions usually resolve.

Fig. 9.26: Lichenoid reaction

Contact allergy with allergens such as cinnamon-flavoring agent, peppermint, dental restorative materials (amalgam, mercury, copper, gold, nickel, and composites), and denture acrylic has been reported to cause oral lichenoid lesions.

Oral lichenoid lesions have been found in HIV-positive individuals, apparently as a result of administration of zidovudine and/or ketaconazole. Oral lichenoid lesions have also been described following ingestion of the street drug, crystal methamphetamine. Hepatitis C is a systemic condition that has been implicated with induction of oral lichenoid lesions.

Some of the drugs that have been shown to cause oral lichenoid lesions include anti-malarials (chloroquine), anti-arthritic drugs (penicillamine), nonsteroidal antiinflammatory drugs (NSAIDs), antihypertensive drugs (ACE inhibitors), and antidiabetic drugs (tolbutamide, chlorpropamide). However, associations between oral lichen planus and systemic diseases may be co-incidental as oral lichen planus is relatively common, it occurs predominantly in older individuals, and drugs used in the treatment of systemic diseases trigger oral lichenoid lesions. As an example, the oral lichenoid lesions in "Grinspan's syndrome" (triad of oral lichen planus, diabetes mellitus and hypertension) may be a reaction to the drugs used to treat diabetes mellitus or hypertension.

The clinical features of oral lichenoid lesions are similar to that of oral lichen planus. The diagnosis of oral lichen planus and oral lichenoid lesions is made by histopathological examination. Three characteristic features of oral lichen planus are seen histopathologically:

1. Hyperparakeratosis or hyperorthokeratosis
2. A band like layer of chronic inflammatory cells (T cells) within the underlying connective tissue
3. Liquefaction degeneration of the basal keratinocytes

In comparison, oral lichenoid lesions cannot always be distinguished from oral lichen planus but may show a deep, as well as superficial infiltrate of T cells, rather than the classic band like infiltrate of oral lichen planus.

Treatment of oral lichenoid lesions can be variable. If the patient has been using flavoring

agents, they should be advised to discontinue the use of such products. Unlike true lichen planus, drug-induced oral lichenoid lesions disappear after drug withdrawal, removal or changing of the drug. Withdrawal, removal or changing of the drug should be considered after consultation with the patients physician.

Some physicians may be reluctant to change a patients medication, particularly when that drug has been proved beneficial in controlling life threatening disease such as diabetes mellitus, and hypertension.

Recurrent Aphthous Ulcers

Recurrent aphthous ulcers (RAU) are a common condition in which recurring round ulcers affect the oral mucosa. Recurrent aphthous ulcers are also called recurrent aphthous stomatitis or canker sores. It is one of the most painful oral mucosal inflammatory ulcerative conditions and can cause pain on eating, swallowing and speaking.

Clinical Features

Recurrent aphthous ulcers are more commonly seen in young adults below 30 years of age. It affects women more often than men.

Clinical Presentation

The ulcers are painful, clearly defined, round or oval, with a shallow necrotic center covered with a yellow-grayish pseudomembrane and surrounded by raised margins and erythematous haloes. The pain lasts for three to four days following which epithelialization can occur.

An important point to remember is that RAU typically do not have a prodrome of fever, malaise and vesicle formation, there is no associated gingival erythema, and the RAU occur almost exclusively on movable oral mucosa, such as the buccal mucosa, labial mucosa, tongue, and soft palate. However, RAU are characterized by a prodrome of localized burning sensation for 24 to 48 hours that can precede the ulcers.

Classification

Recurrent aphthous ulcers have three clinical presentations, which are as follows:

1. Minor RAU
2. Major RAU
3. Herpetiform RAU

Minor Aphthous Ulcers

Minor aphthous ulcers (Mikulicz's aphthae or mild aphthous ulcers) account for majority of all cases of recurrent aphthous ulcers. Minor aphthous ulcers can involve every non-keratinized mucosa of the oral cavity. However, they usually involve the labial and buccal mucosa (Fig. 9.27), the floor of the mouth and the ventral or lateral surface of the tongue (Fig. 9.28). They are smaller than 1 cm in diameter and tend to heal slowly within 10 to 14 days without scarring.

Fig. 9.27: Minor recurrent aphthous ulcer involving the left buccal mucosa

Fig. 9.28: Minor recurrent aphthous ulcers involving the lateral border of tongue

Major Aphthous Ulcers

Major aphthous ulcers (periadenitis mucosa necrotica recurrens, ulcerative stomatitis and Sutton's disease) account for 10 to 15% of all cases of recurrent aphthous ulcers. The prodromal symptoms are more intense than those of minor aphthous ulcers. They are large solitary or multiple, chronic, deep crater-like, painful ulcerations that extend through the epithelium into the connective tissues and tend to involve nonkeratinized oral mucosa (lips, soft palate, and throat) overlying the minor salivary glands but can present in any location (Fig. 9.29). They are larger than 1 cm in diameter and can lasts for weeks or months and often leave a scar after healing.

Fig. 9.29: Major recurrent aphthous ulcer in HIV patient

Herpetiform Aphthous Ulcers

Herpetiform aphthous ulcers account for only 5 to 10% of all cases of recurrent aphthous ulcers. Multiple (5 to 100) 1 to 3 mm small, rounded, painful ulcers resembling ulcers of herpes simplex are seen anywhere on the oral mucosa. They tend to fuse and produce much larger ulcers lasting for 10 to 14 days.

Etiology

The etiology is probably multifactorial, with various predisposing factors (Table 9.3), which provoke a cell-mediated immune response.

Table 9.3: Predisposing factors

• Trauma
• Stress
• Foods
• Hormonal imbalance

Genetic Basis

There is often a genetic basis for recurrent aphthous ulcers. The probability of recurrent aphthous ulcers is 90% when both parents are affected, but only 20% when neither parent has recurrent aphthous ulcers. It is also likely to be more severe and tends to start at an earlier age in patients with a positive family history than in those without a positive family history.

Immunopathogenesis

The immunopathogenesis of recurrent aphthous ulcer is very much similar to that of oral lichen planus, except the keratinocyte lysis occurs throughout all strata and is not restricted to the basal cell layer as seen in oral lichen planus. The preulcerative stage is characterized by lymphocytic infiltrate composed of CD8+ T cells and natural killer (NK) cells in response to oral keratinocyte-associated antigens. Tumor necrosis factor released by CD8+ T lymphocytes results in lysis of keratinocytes followed by a localized papular swelling surrounded by reactive

erythematous halo representing vasculitis. The papule then ulcerates and is covered by a fibrinous membrane. Finally, there is healing with epithelial regeneration.

Diagnosis

The diagnosis of recurrent aphthous ulcers is made on the basis of history and clinical examination since there are no specific laboratory tests available. Various laboratory tests should be carried out, which include complete blood picture, serum iron, folate, and vitamin B_{12}.

Hemoglobin levels and red blood cell counts are generally within normal range in patients with recurrent aphthous ulcers. However, patients with recurrent aphthous ulcers reveal deficiency of serum iron, folate and vitamin B_{12}.

A medical history should be taken to rule out systemic disorders associated with recurrent aphthous ulcers (Fig. 9.30). They include:

1. Ulcerative colitis
2. Crohn's disease
3. Reiter's syndrome or Behcet's disease
4. Sweet's syndrome (acute febrile neutrophilic dermatosis)
5. Periodic fever, aphthae, pharyngitis and adenitis syndrome (PFAPA syndrome)
6. Neutropenia
7. HIV infection

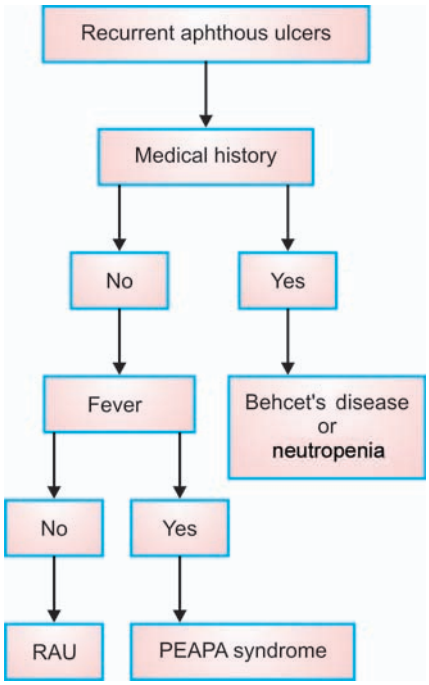

Fig. 9.30: Diagnosis of recurrent aphthous ulcers

Management

There is no definitive treatment of recurrent aphthous ulcers as the etiology is unknown. Some patients have mild outbreaks, whereas others have severe outbreaks. Some patients present with single small ulcer, while others present with multiple small ulcers. Some patients present with large ulcers, while others present with combination of small or large. In some patients, the severity and frequency of outbreaks ease with the passing of years; in others, severity and frequency worsen. Thus, therapy should be tailored to each patient individually. Treatment of recurrent aphthous ulcers is symptomatic and has four major goals:

1. Ulcer management (to promote healing and reduce duration)
2. Pain management (to reduce morbidity and enhance function)
3. Nutritional management (to ensure adequate food and fluid intake)
4. Disease control (to prevent recurrence or reduce frequency)

In all patients with recurrent aphthous ulcers, it is important to rule out predisposing factors and treat them where possible, before introducing specific therapy. In order to determine treatment strategies, the practitioner may classify recurrent aphthous ulcers into three clinical presentations:

Type A

Recurrent aphthous ulcers last for only a few days and occur only few times a year. In this condition, pain is tolerable. The clinician should

Table 9.4: Potential side effects of prednisolone and azathioprine	
Prednisolone	Insomnia, nervousness, increased appetite, indigestion, diabetes mellitus, hirsutism, joint pain, and glaucoma
Azathioprine	Thrombocytopenia, leukopenia, secondary infections, anemia, nausea, vomiting, anorexia, diarrhea, and non-Hodgkin's lymphoma

identify the predisposing factor that causes the ulcer and eliminate it. For example if trauma during tooth brushing has been identified, the clinician can suggest a softer tooth brush and gentle brushing.

Type B

Recurrent apphthous ulcers appear each month, lasting three to ten days. In this condition, pain may or may not be tolerable and the patient may have changed the diet and oral hygiene habits because of the pain. The clinician should identify the predisposing factor that causes the ulcer and eliminate it. It is essential to identify patients who use corticosteroids (if they are indicated for him or her) when they experience prodromal symptoms. Treatment includes the use of chlorhexidine gluconate 0.20% solution and a short course of topical corticosteroid ointment (triamcinolone acetonide) applied directly to the ulcers, four times a day. In patients with stubborn recurrent aphthous ulcers, a short course of systemic corticosteroid therapy may be required. Prednisolone, never exceeding more than 50 mg per day (preferably in the morning) for five days is the ideal choice. If corticosteroids are used, patients should be monitored for superadded oral candidosis. Oral prophylaxis should be considered in patients with poor oral hygiene due to altered oral hygiene habits once the ulcers heal.

Type C

Recurrent aphthous ulcer develops by the time one ulcer heals. Treatment includes the use of topical corticosteroids, systemic corticosteroids (prednisolone, clobetasol, fluticasone or fluocinonide), and immunosuppressants (azathioprine or dapsone). Prednisolone, an anti-inflammatory and an immunosuppressive agent, can be used in combination with topical ointments and rinses. Systemic prednisolone therapy should be started at 1.0 mg/kg a day as a single dose in patients with severe RAS and should be tapered after one to two weeks. Most potential side effects of prednisolone are due to treatment that persists for more than 2 weeks. Prednisolone can be used in combination with another immunosuppressive agent, azathioprine, to reduce the dosage of prednisolone. 50 mg/kg per day for one week azathioprine can be administered safely in combination with prednisolone (Table 9.4) shows the potential side effects of prednisolone and azathioprine. Recurrent aphthous ulcers can be prevented by thalidomide and pentoxifylline, which prevent the synthesis of TNF-α. Thalidomide therapy has been thoroughly researched in HIV-positive patients. One study concluded that HIV-positive patients with recurrent aphthous ulcers benefited from thalidomide therapy. Initial treatment in either HIV-positive or HIV-negative patients should be 100 or 200 mg of thalidomide daily, depending on the severity of the disease and the patients tolerance. Once the lesion resolves, therapy must be stopped until remission occurs. Other treatment modalities include the use of chemical cautery, electrocautery, or lasers to convert the ulcer into a wound. Ultrasound has been suggested to provide a beneficial effect on recurrent aphthous ulcers.

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Chapter 10

HIV/AIDS in Dental Care

CENTRE FOR DISEASE CONTROL AND PREVENTION (CDC) CASE DEFINITION

CDC, in collaboration with Council of State and Territorial Epidemiologists (CSTE), has expanded the AIDS surveillance case definition to include all HIV-infected persons with CD4+ T cell counts of less than 200 cells/µl. In addition to retaining the 23 clinical conditions in the previous AIDS surveillance definition, the expanded definition includes pulmonary tuberculosis (TB), recurrent pneumonia, and invasive cervical cancer. This expanded definition for reporting cases to CDC became effective from January 1, 1993.

Acronym (AIDS)

1. Acquired means you can acquire it
2. Immune deficiency means a weakness in the body's immune system to fight diseases
3. Syndrome means a group of health problems that make up a disease

Epidemiology

Acquired Immunodeficiency Syndrome (AIDS) has killed more than 25 million people since it was first recognized in 1981, making it one of the most destructive epidemics in recorded history. Despite recent, improved access to anti-retroviral treatment and care in many regions of the world, the AIDS epidemic claimed 3.1 million lives in 2005; more than half a million (570 000) were children.

The total number of people living with the human immunodeficiency virus (HIV) reached its highest level: an estimated 40.3 million people (Fig. 10.1) are now living with HIV. Close to 5 (4.9) million people were newly infected with the virus in 2005.

National HIV infection levels in Asia are low compared with some other continents, notably Africa. Diverse epidemics are underway in India, where an estimated 5.1 million Indians were living with HIV in 2003 (NACO, 2004a). Although levels of HIV infection prevalence appear to have stabilized in some states (such as Tamil Nadu, Andhra Pradesh, Karnataka and Maharashtra), it is still increasing in at-risk population groups in several other states. As a result, overall HIV prevalence has continued to rise.

In India, the National AIDS Control Organization (NACO), established in 1992, is responsible for coordinating the overall health sector response to HIV/AIDS, supported by the state AIDS control societies at the state level. The National AIDS Control Programme, first launched in 1987, is now in its second phase of implementation (1999–2006). Its objective is to reduce the transmission of HIV through a

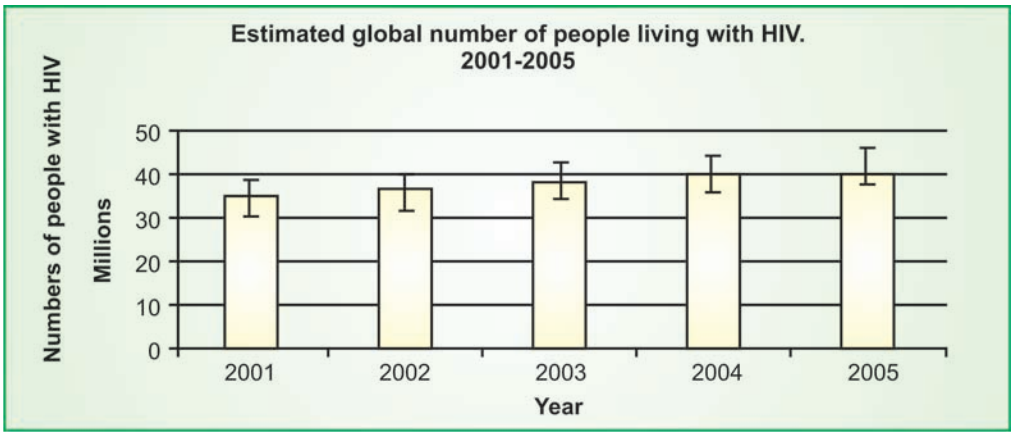

Fig. 10.1: Epidemiology

decentralized and comprehensive programme of generating awareness, changing behavior, targeting vulnerable groups with intervention and conducting research.

Historical Background

Dr. Luc Montagnier (1983) of Pasteur Institute, Paris, first identified and named it Lymphadenopathy Associated Virus. Dr. Roberto Gallo identified it later at NIH Bethesda, Maryland, U.S.A in 1984 and named it as Human T cell Lymphotropic Virus.

Causative Organism

AIDS is caused by a retrovirus called Human Immune Deficiency Virus (HIV). It measures about 90-100 nm in diameter and is lymphotropic.

Structure of HIV (Fig. 10.2)

The HIV-1 virion is spherical in shape with an outer viral envelope with gp120 and gp41 proteins. The viral core is surrounded by a matrix p17 protein. The viral core contains the capsid

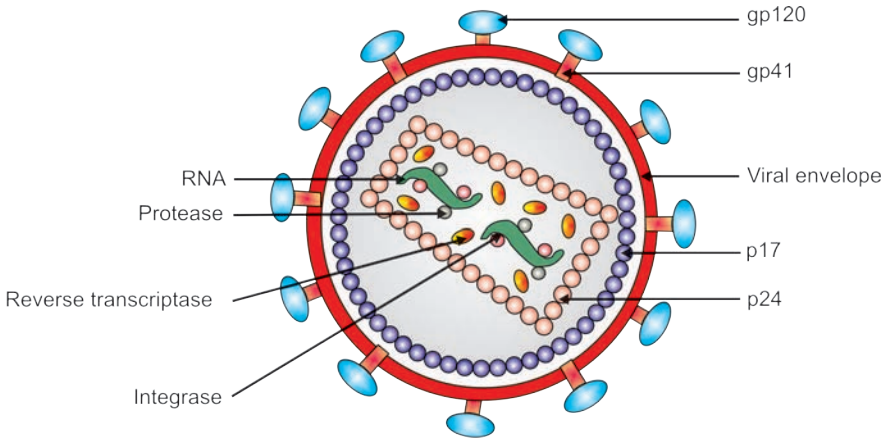

Fig. 10.2: Structure of HIV

p24 protein, 2 copies of RNA, and 3 viral enzymes (reverse transcriptase, protease, and integrase).

HIV Genome

The HIV genome contains *gag*, *pol* and *env* genes (Fig. 10.3), which encode various viral proteins:

1. ***gag*** gene encodes—matrix protein p17 and capsid protein p24
2. ***pol*** gene encodes—reverse transcriptase, protease and integrase
3. ***env*** gene encodes—viral envelope proteins gp120 and gp41

Classification of HIV

HIV is a highly variable virus, which mutates very readily, which means there are many different strains of HIV, even within the body of a single infected person. Based on genetic similarities, the numerous virus strains may be classified into types, groups, and subtypes. There are 2 genetically different types of HIV: HIV-1 and HIV-2. Both types are transmitted by sexual contact, through blood, and from mother to child, and they cause AIDS.

However, it seems that HIV-2 is less easily transmitted, and the period between initial infection and illness is longer in the case of HIV-2. The relatively uncommon HIV-2 type is mostly confined to West Africa and is rarely found elsewhere. Worldwide, the predominant virus is HIV-1, and in general when people refer to HIV without specifying the type of virus they will be referring to HIV-1. The rest of this chapter will relate to HIV-1 and diseases caused by it, but are generally applicable to HIV-2 as well. The strains of HIV-1 can be classified into three groups:

1. **Major group designated as M**: More than 90% of HIV-1 infections belong to HIV-1 group M. Within group M there are known to be at least nine genetically distinct subtypes (clades). These are subtypes A, B, C, D, E, F, G, H, J. The clades differ from each other by their geographic distribution. For example, subtype C is largely predominant in southern and eastern Africa, India, and Nepal
2. **Outlier group designated as O**: Group O appears to be restricted to west-central Africa
3. **New group designated as N**: Group N-discovered in 1998 in Cameroon is extremely rare

Transmission of HIV (Fig. 10.4)

1. Sexual (homosexuals/heterosexuals)
2. Parenteral (intravenous drug abusers/hemophiliacs)
3. Mother to infant (vertical transmission)
   a. Transplacental
   b. During delivery
   c. HIV infected milk

HIV Is Not Transmitted Through

1. Saliva
2. Kissing
3. Mosquito bite
4. Touching
5. Sharing toilets

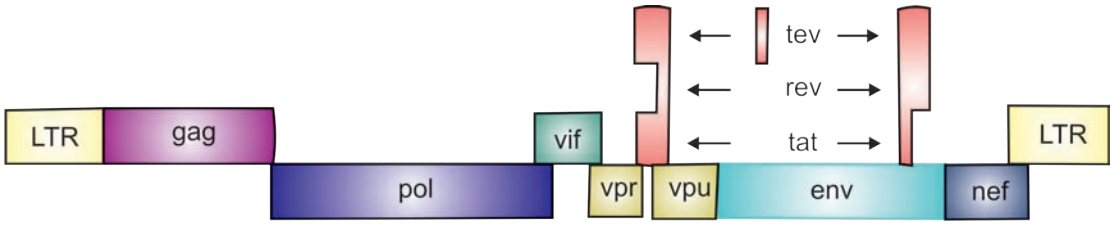

Fig. 10.3: HIV genome

Fig. 10.4: Routes of transmission of HIV

Saliva: Saliva contains a protein called "secretary leukocyte proteinase inhibitor" which inactivates the HIV. Antibodies (IgA) are present in the saliva against HIV.

Mosquitoes: The first reason why mosquitoes do not transmit HIV is that the virus is present at very low levels in the blood of HIV positive individuals. The second reason is that even the HIV is digested along with the blood. The third reason is that the feeding apparatus of the mosquito has two separate passages, one for the saliva and the other for the blood. Thus, the mosquito delivers the saliva through one passage and sucks the blood through the other in a unidirectional manner.

In order for a mosquito to transmit HIV from an infected person to an uninfected, host:

1. The levels of HIV in the circulating blood should be high
2. They should survive in the mosquito
3. The feeding apparatus of a mosquito should be like a hypodermic needle

Life Cycle of HIV (Fig. 10.5)

The target cells of HIV are the CD4 (where CD4 is cluster of differentiation or cluster designation) cells, which include dendritic cells (Langerhans cells) macrophages and CD4+ T cells ("master cell"). CD4 is a docking molecule present on the macrophages, Langerhans' cells, and CD4+ T cells and is a high-affinity receptor for HIV. This explains the tropism of the virus for the CD4+ T cells, macrophages, and Langerhans' cells.

However, binding to CD4 is not sufficient for infection. The HIV envelope gp120 must also bind to coreceptors to enter the cell. There are two coreceptors: CCR5 and CXCR4. The CCR5 coreceptor is present on the macrophages,

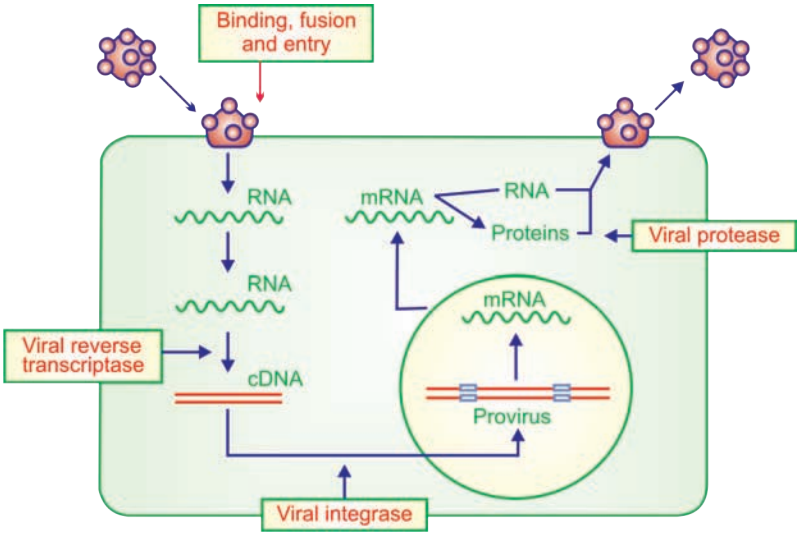

Fig. 10.5: An overview of lifecycle of HIV

monocytes, and CD4+ T cells and the CXCR4 coreceptor is present only on the CD4+ T cells. The life cycle of HIV can be divided into four stages: Entry, reverse transcription and integration, transcription and translation, and assembly, budding and maturation.

Entry

The process typically begins when a HIV particle bumps into CD4+ T cell, a cell that carries on its surface a special docking molecule called CD4. The gp120 on the surface of the virus particle binds to the CD4. This binding leads to conformational change in the gp120 following which CD4 and gp120 bind to CCR5. The gp41 protein then binds and fuses with the cell membrane. After fusion, the contents of the HIV are then released into the cell, leaving the envelope behind.

Reverse Transcription and Integration

Once inside the cell, the HIV enzyme reverse transcriptase converts the viral RNA into proviral cDNA (complementary DNA), which is compatible with human DNA. This cDNA is transported to the nucleus, where it is integrated into the human DNA by the enzyme integrase. Once integrated, the HIV DNA is known as a provirus.

Transcription and Translation

The provirus may remain dormant (non-transcribed) within a cell for a long time (months or years) and the HIV infection becomes latent. It is important to note that although HIV can infect resting CD4+ T cells, the transcription of provirus occurs only when the infected cell becomes activated by exposure to antigens (e.g., microbes) or cytokines. Once the infected cell becomes activated, the provirus is transcribed into messenger RNA (mRNA). The mRNA is transported outside the nucleus into the cytoplasm where it is translated to produce viral RNA, viral proteins, and the enzyme protease. The viral RNA forms the genetic material for the next generation of viruses.

Assembly, Budding and Maturation

The viral RNA and viral proteins assemble at the cell membrane, following which the enzyme protease chops up long strands of proteins into smaller pieces, which are used to construct mature viral cores. The viral core fuses with the cell membrane and buds out from the cell, taking a bit of the cell membrane to form a new viral envelope. The newly matured HIV particles are ready to infect another CD4+ T cell and begin the replication process all over again. It has been estimated that 100 billion new viral particles are produced every day, and 1 to 2 billion CD4+ T cells die each day.

Course of HIV Infection (Fig. 10.6)

1. Early "acute" Phase
2. Middle "chronic" Phase
3. Final "crisis" Phase

Early "Acute" Phase

The early "acute" phase represents the initial response of the immune system to HIV infection. Clinically, this self-limiting illness develops in 50 to 70% of adults 3 to 6 weeks after infection and is characterized by flu-like symptoms, which include fever, malaise, generalized lymphadenopathy, pharyngitis, headache, myalgia, arthralgia, skin rash, and sometimes aseptic meningitis.

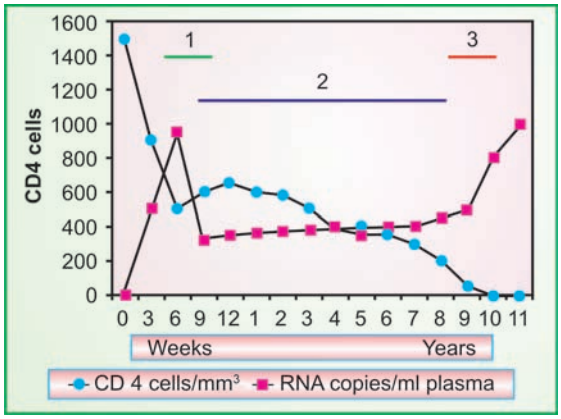

Fig. 10.6: Course of HIV infection

During this phase, HIV initially infects CD4+ T cells and macrophages directly or is carried to regional lymph nodes by Langerhans cells where these cells are present. Viral replication in the regional lymph nodes leads to viremia (high levels of viral particles in the blood) and widespread seeding of HIV in the lymphoid tissues (lymph nodes, spleen, and tonsils) resulting in reduction of CD4+ T cell count. The viremia is controlled by the development of antiHIV antibodies (usually within 3 to 12 weeks). As viremia dies away, CD4+ T cell count returns to normal number.

Middle "Chronic" Phase

The immune system is stable. Patients are usually asymptomatic or develop persistent lymphadenopathy, and many patients have minor opportunistic infections such as oral candidosis or shingles. The virus replicates in the CD4+ T cells and macrophages present in the lymphoid tissues for several years and gradually destroy the CD4+ T cells. However, when the CD4+ T cells that are destroyed cannot be replenished, the CD4+ T cell count decreases and the patient enters the final crisis phase. The macrophages are not destroyed by the virus replication and they transport the virus to various tissues, particularly the brain.

Final "Crisis" Phase

This phase is characterized by the appearance of opportunistic infections and specific conditions as outlined by CDC (Table 10.1). Approximately 90% of patients with untreated AIDS die from opportunistic infections. Patients with AIDS often have generalized lymphadenopathy, severe weight loss, fatigue, chronic diarrhea, chronic fever, and night sweats. Laboratory tests reveal increased viral load (suggestive of viremia), altered CD4/CD8 ratio, and decrease

in CD4+ T cell count. The number of CD4+ T cells decrease from a normal range of 1500 to 200 cells/mm^3. The normal CD4+ T cell/CD8+ T cell ratio is about 2. In AIDS patients, it is $\leq$ 0. 5 and therefore the ratio is an important measure of the disease progression. Thus, as the disease progresses the number of CD4+ T cells decrease and CD8+ T cells increase. The marked reduction of CD4+ T cells explains the lack of immune response and is most likely related to the increase in malignant disease associated with AIDS.

Causes for Decreased CD4+T-lymphocyte Count

1. Because of HIV infection.
2. Killing of infected CD4+ T cells by CD8+ T cells
3. Formation of syncytia (giant cells) by fusion of infected CD4+ T cells and uninfected CD4+ T cells
4. Uninfected CD4+ T cell may bind to free gp120 resulting in apoptosis
5. Depletion of CD4+ T cell precursor cells, either by direct infection of thymus cells or by infection of cells that secrete cytokines essential for CD4+ T cell differentiation

Consequences of CD4+ T-cell ("Master Cell") Destruction

1. Decreased antigen presentation by macrophages
2. Decreased antibody production by plasma cells in response to antigen
3. Decreased killing of tumor cells by Natural Killer (NK) cells
4. Decreased CD8+ T cell cytotoxicity
5. Decreased response to antigen and decreased cytokine production by CD4+ T cells

Oral Manifestations

Oral lesions are frequently associated with HIV infection. Oral lesions associated with HIV infection, also occur in other conditions

Table 10.1: Diagnostic criteria for AIDS

AIDS is diagnosed when an individual with HIV develops at least one of these conditions:

1. CD4+ T cell count drops below 200 cells/mm^3
2. Development of one of the following opportunistic infections:
   - **Fungal:** Candidosis of bronchi, trachea, lungs, or esophagus; *Pneumocystis carinii* pneumonia; histoplasmosis (disseminated or extrapulmonary)
   - **Viral:** Cytomegalovirus disease (other than liver, spleen, or nodes); cytomegalovirus retinitis (with loss of vision); herpes simplex with chronic ulcers (greater than 1 month's duration), or bronchitis, pneumonitis, or esophagitis; progressive multifocal leukoencephalopathy; extrapulmonary cryptococcosis
   - **Protozoal:** Coccidioidomycosis (disseminated or extrapulmonary), toxoplasmosis of brain; chronic intestinal isosporiasis (greater than 1 month's duration); chronic intestinal cryptosporidiosis (greater than 1 month's duration)
   - **Bacterial:** *Mycobacterium tuberculosis* any site (pulmonary or extrapulmonary); *Mycobacterium avium* complex or *Mycobacterium kansasii* (disseminated or extrapulmonary); recurrent pneumonia; *Recurrent salmonella* septicemia
3. Development of one of the following opportunistic cancers:
   - Invasive cervical cancer; Kaposi's sarcoma; Burkitt lymphoma; lymphoma immunoblastic; lymphoma primary of the brain
4. Wasting syndrome occurs: Defined as loss of 10% or more of ideal body mass
5. Dementia

characterized by immunosuppression. Many HIV related oral lesions occur early in HIV infection. Thus, early detection of associated oral lesions should, in many cases, result in earlier diagnosis of HIV infection. HIV related oral lesions could be broadly classified into four categories: infections (bacterial fungal and viral), neoplasms, immune-mediated, and others (xerostomia, pain syndromes, and nutritional) (Table 10.2).

Table 10.2: Oral lesions associated with AIDS

Bacterial infections: Linear erythematous gingivitis; necrotizing ulcerative periodontitis; necrotizing stomatitis; actinomycosis; bacillary epitheloid angiomatosis
Fungal infections: Oral candidosis; angular cheilitis or angular cheilosis; cryptococcosis; histoplasmosis; aspergillosis; mucormycosis; geotrichosis
Viral infections: Herpes simplex virus infection; shingles; oral hairy leukoplakia; oral warts; focal epithelial hyperplasia; condyloma acuminatum
Neoplasms: Squamous cell carcinoma; Kaposi's sarcoma; non-Hodgkin lymphoma
Others: Bell's palsy; recurrent aphthous ulcers; xerostomia; parotid gland enlargement ; pain syndromes; immune thrombocytopenic purpura; melanotic pigmentation; trigeminal neuropathy

Linear Eythematous Gingivitis

Linear erythematous gingivitis or linear gingival erythema appears as an erythematous distinctive linear band (1-3 mm wide) at the free gingival margin, often with petechiae. It is typically associated with no symptoms and in most cases, gentle probing produces bleeding. Unlike conventional gingivitis, linear erythematous gingivitis is not significantly associated with plaque and can be seen in patients with excellent oral hygiene. Therefore, linear gingival erythema usually does not respond and persists following conventional periodontal therapy (dental prophylaxis). There is no evidence to suggest that this entity will proceed to the far more destructive necrotizing periodontitis.

Histological examination fails to reveal any significant inflammatory response, suggesting that the lesions represent an incomplete (aborted) inflammatory response, principally with only hyperemia present. Treatment includes intensive daily oral hygiene, oral rinsing with chlorhexidine gluconate 0.20% solution, scaling and root planing (if necessary) with 10% betadine solution irrigation, and careful follow-up and maintenance.

Nectrotizing Ulcerative Periodontitis (NUP)

This unique periodontal lesion is characterized by pain, generalized gingival erythema that is often associated with spontaneous bleeding, interproximal gingival necrosis, cratered soft tissues, deep osseous pain in the jaws, and rapidly progressive destruction of the periodontal attachment and bone (Fig. 10.7).

Destruction of the periodontal attachment and bone can be extremely rapid and extensive and may result in as much as 90% bone loss around isolated teeth in as few as 12 weeks. If left untreated, NUP may extend into the adjacent tissues and expose the alveolar or palatal bone and the condition has been called necrotizing

Fig. 10.7: Necrotizing ulcerative periodontitis

stomatitis. NUP adversely affects oral intake of food, resulting in significant and rapid weight loss. The diagnosis of NUP should be made based on distinctive clinical characteristics.

Treatment includes oral rinsing with chlorhexidine gluconate 0.20% solution, intrasulcular lavage or irrigation with 10% betadine solution, antibiotic regimen of 250 mg metronidazole 3 times per day for 5 to 7 days, often combined with 250 mg amoxicillin-clavulanate potassium 3 times a day for 5 to 7 days. As systemic antibiotics increase the patients risk of developing oral candidosis, concurrent administration of an antifungal agent should be considered. Careful follow-up or frequent appointments are appropriate and recommen-ded in the acute and healing stages of NUP to perform the necessary periodontal therapies (e.g., scaling and root planing), to assess tissue response, and to monitor the patients oral hygiene performance.

Oral Candidosis

The most common HIV-related soft-tissue lesion is acute pseudomembranous oral candidosis (reported in approximately 75% of cases), predominantly due to *Candida albicans*, a normal inhabitant of the oral cavity in healthy individuals. The following forms of oral candidosis have been frequently associated with HIV infection: acute pseudomembranous, acute erythematous and angular cheilitis. Angular cheilitis, though prevalent in HIV-infected individuals, is also seen in individuals who do not have HIV infection. Chronic hyperplastic type has been described, but this finding is rare.

In individuals infected with HIV, the development of oral candidosis may be an indication of immune deterioration and has prognostic significance for the development of AIDS. Oral candidosis may precede other signs of immune deficiency and is one of the clinical indicators for initiating and continuing prophylaxis for *Pneumocystis carinii* pneumonia. Diagnosis of oral candidosis should be made by identification of clinically distinctive lesions, by microscopic examination of cytological smears or biopsy tissue, or by response to antifungal therapy.

Treatment of oral candidosis is determined by the clinical type, distribution, and severity of infection. Clotrimazole 1% w/v–(Candid mouthpaint 15 ml) is effective for limited and accessible lesions. Patients should be instructed to maintain proper oral hygiene in order to prevent caries that may result from the high sugar content in nystatin and clotrimazole. The use of topical fluoride therapy should be considered for patients taking such medication for extended periods. When oropharyngeal candidosis cannot be controlled with topical medication alone, systemic antifungal therapy should be initiated.

Systemic antifungal therapy for oral candidosis involves the use of ketoconazole, fluconazole, and itraconazole antifungal medications. Fluconazole (100 mg tablet, 1 tablet a day) is an excellent systemic antifungal medication with a favorable therapeutic index, making it the preferred systemic antifungal medication. A typical antifungal treatment course should be for 10 to 14 days, with use of the antifungal agent continued even after clinical signs and symptoms of oral candidosis have been resolved. Because patients with reduced salivary flow are more susceptible to developing oral candidosis, salivary flow should be stimulated to help reduce the incidence and severity of oral candidosis. Chewing sugarless gum in the mouth can accomplish salivary flow stimulation.

Herpes Simplex Infection

In immunocompetent patients, oral ulcers caused by the herpes simplex virus (HSV) occur in

primary infection form (primary herpetic gingivostomatitis) and recurrent forms (recurrent herpes labialis and recurrent intraoral herpes). The primary infection most commonly occurs in children but also may occur in adults.

Recurrent HSV infection represents reactivation of latent virus and not reinfection of HSV. Recurrent HSV infections can either occur as recurrent herpes labialis (RHL) or recurrent intraoral herpes (RIH). The characteristic clinical appearance of RHL is focal clustering of vesicles. The vesicles quickly rupture, resulting in ulcers that coalesce to form the larger irregular-shaped ulcers with a crusted surface. In a healthy individual, the lesions heal without scarring within 7 to 14 days.

Recurrent intraoral herpes (RIH) lesions begin as clusters of tiny vesicles that rupture quickly, resulting in erosions or ulcers without crusting. The RIH lesions involve keratinized mucosa (hard palate, attached gingiva, and edentulous ridges). However, in immunocompromised patients e.g., AIDS, the tongue can also be affected. The lesions on the tongue exhibit mucosal erosions, each of which is surrounded by a circinate, raised, yellow border. This border represents the advancing margin of active viral destruction. Intraoral recurrence follows a pattern of presentation similar to that of RHL except the lesions are intraoral, and crusting does not occur. The pain associated with RIH may interfere with eating and speaking. In a healthy individual, the lesions heal without scarring within 7 to 14 days.

In patients with HIV infection who have marked immune deficiency, ulcers caused by herpes simplex infection tend to be persistent, superficial (infecting the epithelium and not connective tissue), and painful. Persistent herpetic lesions in HIV infected patients that do not resolve after 4 weeks fulfill the Centers for Disease Control and Prevention (CDC) criteria for a diagnosis of AIDS.

These ulcers do not have a characteristic clinical appearance and may appear to be similar to ulcers caused by other agents or circumstances. These ulcers differ from herpes simplex ulceration in immunocompetent individuals in that they are larger, can occur anywhere in the oral cavity, present for longer periods, and are non-responsive to routine therapy. The pain associated with persistent herpetic ulceration can result in reduced oral intake of food and significant weight loss.

As atypical herpetic ulcers may be the first sign of immunosuppression, patients with these ulcers who are not known to be HIV infected should be referred for HIV counseling and testing.

Diagnosis of typical herpes simplex infection includes Tzanck test (mucosal smear), tissue biopsy, viral culture, serology, polymerase chain reaction and response to acyclovir are recommended options to accurately diagnose the ulcers.

Intraoral HSV infection responds well to systemic acyclovir, (200 mg capsules, 1-2 capsules, 5 times a day for 10 days). However, the incidence of acyclovir-resistant HSV has increased among patients with HIV infection. For most of these cases, oral famciclovir and valacyclovir and intravenous foscarnet alone or in combination are effective.

Oral Hairy Leukoplakia (Greenspan lesion)

The term "oral hairy leukoplakia" is unfortunate for several reasons. First of all, oral hairy leukoplakia is a definable lesion as per WHO Collaborating Centre on oral manifestations of the immunodeficiency virus (1993). Furthermore, the lesion is not a premalignant one. Therefore, the use of the term oral hairy leukoplakia should be abandoned. As an alternative, the term "Greenspan lesion" has been suggested by Waal van der I (1996).

It appears as an asymptomatic adherent white patch with vertical corrugations, most commonly on the lateral borders of the tongue. It may be confused with chronic hyperplastic oral candidosis and is predominantly found in homosexual males. Oral hairy leukoplakia (Fig. 10.8) has since been shown to be associated with a localized Epstein-Barr virus (EBV) infection and occurs most commonly in individuals whose CD4+ T cell count is less than 200/mm^3.

Fig. 10.8: Oral hairy leukoplakia

As in all patients, when an HIV infected patient presents with a white lesion on the lateral border of the tongue that cannot be diagnosed because of its clinical appearance, biopsy and microscopic examination should be considered. Oral hairy leukoplakia generally does not require treatment.

Oral Warts

In some patients with HIV infection, human papilloma virus causes a focal epithelial and connective tissue hyperplasia, forming an oral wart. Diagnosis of human papilloma virus lesions should be made by routine biopsy and histological examination.

Major Aphthous Ulcers

Major aphthous ulcers (periadenitis mucosa necrotica recurrens, ulcerative stomatitis, Sutton's disease) account for 10 to 15% of all cases of recurrent aphthous ulcers. The prodromal symptoms are more intense than those of minor aphthous ulcers. They are large solitary or multiple, chronic, deep crater-like, painful ulcerations that extend through the epithelium into the connective tissue. As in non-HIV-infected patients, these ulcers generally occur on nonkeratinized oral mucosa (lips, soft palate, and throat) overlying the minor salivary glands but can present in any location.

They are larger than 1 cm in diameter and can lasts for weeks or months and often leave a scar after healing. Major aphthous ulcers are the most common immune-mediated HIV-related soft-tissue oral lesions, with a prevalence of approximately 2–3% (Fig. 10.9).

Fig. 10.9: Major aphthous ulcer

Diagnosis of aphthous ulcers should be based on the characteristic clinical appearance of painful, round to oval, yellow to white ulcers surrounded by a halo of erythema. They often last much longer and are less responsive to therapy.

The management of aphthous ulcers should include the use of topical corticosteroids; however, caution should be taken because steroid use may result in oral candidosis, therefore, concurrent administration of an antifungal agent should be considered.

Treatment requires the use of a potent topical corticosteroid when the lesion is accessible or corticosteroid steroid mouthwash (dexamethasone 3 times daily, rinse for 45 seconds and expectorate) when the lesion is inaccessible.

When multiple ulcers are present or response to topical treatment is incomplete, systemic corticosteroid therapy is required (1-2 mg/kg a day divided in 4 doses) may be necessary. Systemic corticosteroid therapy should be given for 5-7 days, with gradual tapering of the dose over 2 weeks.

Thalidomide has been shown to be effective for the treatment of non-resolving aphthous ulcers in HIV-positive patients Because of severe side effects, thalidomide should only be used when all other options have been exhausted. In adolescent and adult women capable of bearing children, thalidomide should only be used when the woman is known not to be pregnant and is using effective methods of birth control.

However, if the ulcers are thought to be drug induced, the medication should be temporarily discontinued or dose reduced. Medications that can cause aphthous ulcers include zidovudine, and foscarnet.

Diagnosis

The diagnosis of HIV infection is usually made on the basis of the detection of antiHIV antibodies. Serological tests for detecting antiHIV antibodies are generally classified as screening tests (initial tests) or confirmatory tests (supplemental tests).

Screening tests help in the likely identification of antiHIV antibodies, and confirmatory tests are used to confirm whether the antiHIV antibodies found are reactive with proteins specific to antiHIV antibodies.

The most widely used screening test is the ELISA as it is most appropriate for screening large numbers of specimens on a daily basis, e.g., blood donations and the most widely used confirmatory test is the Western Blot. The key points in the diagnosis of HIV are as follows:

1. HIV disease is diagnosed by the presence of clinical signs and symptoms and specific laboratory tests
2. The ELISA (enzyme-linked immunosorbent assay) is the screening test used to diagnose HIV infection
3. The Western blot and PCR (polymerase chain reaction) tests help to confirm HIV infection
4. Maternal antibodies are present in an infant's blood for up to 18 months after birth, making it difficult to establish the diagnosis of HIV by ELISA and Western blot
5. The CDC has established a staging system for HIV disease in infants and children based on the CD4+ T cell count and clinical signs and symptoms
6. The WHO clinical diagnostic system is based on dividing signs and symptoms into major and minor criteria
7. Diagnosing HIV follows the same principles in adults as in children.

Diagnostic Tests

ELISA

One screening test used to diagnose HIV is the ELISA (enzyme-linked immunosorbent assay), which is an enzyme immunoassay (EIA). When this test is performed on a patients serum or blood, it identifies antiHIV antibodies. ELISA tests are highly sensitive but not always specific. This means that other illnesses besides HIV can cause a positive test. Among these illnesses are autoimmune diseases, certain viral infections, syphilis, and hematological malignancies. Pregnancy may also cause a false-positive ELISA. As maternal antibodies are present in an infant's blood for up to 18 months after birth, the ELISA

is accurate only in children over 18 months of age. Further, because the test is based on the detection of antiHIV antibodies, an infected patient may have a negative ELISA during a "window period".

Window Period

The window period is the time between initial infection with HIV and the development of enough antiHIV antibodies to be detected through testing. In general, 3 to 3 months (12 weeks) is required after infection. A recently infected individual, therefore, may not test positive for HIV but could still transmit HIV to others.

The virus is not latent during the window period. Viral replication in the regional lymph nodes leads to viremia (high levels of viral particles in the blood) and widespread seeding of HIV in the lymphoid tissues (lymph nodes, spleen, and tonsils) resulting in reduction of CD4+ T cell count. In fact, the viral load (number of HIV RNA copies per mL of blood plasma) is higher after initial infection than any period until advanced HIV disease. Understanding the window period is important for recommendations regarding for risk prevention and further testing as mentioned below:

1. Persons should be counseled to take precautions to prevent transmission of HIV during the window period
2. A recently exposed person should be advised to return for antiHIV antibody testing within 3 weeks after the exposure incident
3. It is important to ensure that persons receiving pre-HIV test counseling and post-HIV test counseling understand the window period concept.

Western Blot

A western blot is a polyacrylamide gel electrophoresis that detects bands of proteins specific to antiHIV antibodies. If no bands are seen, the western blot is negative. If most or all of the protein bands are seen, the western blot is positive. The western blot test can be inconclusive. In the event that an inconclusive test result is found, the test should be repeated on the same serum sample and then repeated again in two weeks. If the inconclusive pattern persists, the western blot needs to be repeated periodically for the next six months. If the pattern persists after six months, the person is most likely not infected with HIV.

Rapid Tests

Rapid HIV screening tests, first approved in 1996, can be performed in an average of 10 minutes. Several rapid tests detect antiHIV antibodies, much like the ELISA and are as accurate as ELISA. The results are available in just a few minutes to hours. Most rapid tests can be performed on blood obtained from a finger stick and performing them requires little training. Many different commercial rapid tests are available, and most are 99-100% sensitive and specific. Rapid test methods include "dot blot" or "immunoblot" assays that produce a colored dot on the solid phase surface. Some rapid tests can use saliva or urine samples instead of blood samples.

For positive-tests, however, a confirmatory ELISA and Western blot is still required to eliminate false-positives. Like the ELISA, these rapid tests are accurate only in children over 18 months of age and usually give a negative result during the window period.

DNA/RNA PCR

Finally, polymerase chain reactions (PCR) for the DNA or RNA of the HIV virus can be performed. These tests are highly sensitive and specific for HIV infection. They are often used if the results of other diagnostic tests are unclear. DNA PCR is most commonly utilized to diagnose HIV infection in children under the age of 18 months.

Test Counseling

Pretest Counseling

The pretest counseling consists of a process starting with asking history of exposure to risk factors and an explanation of preventive measures. Information about the test, including an explanation about what the test can and cannot determine is also necessary. However, pretests require consent prior to testing because of the emotional, physical, and social implications of having a diagnosis of HIV infection.

Post-test Counseling

Post-test counseling should be performed with all patients who return for test results.

Seronegative post-test counseling should include:

1. Reinforce to avoid risk factors for the prevention of HIV transmission
2. Confirm whether the last possible exposure was not within the last six months. If it was, encourage retesting 3 weeks to 3 months after the most recent exposure
3. Provide information on community support services
4. Provide information on psychosocial support, if appropriate

Seropositive post-test counseling should include:

1. Assess the individual for mental distress
2. Assess the availability of personal support (friends, family, etc.)
3. Discuss plan for partner notification
4. Persons should be counseled for eliminating or reducing the risk of transmission to others
5. Review basic principles of good health such as nutrition, stress reduction, sleep and exercise, and good dental care
6. Discuss the importance of avoiding additional infections that will stress the immune system e.g., candidosis
7. Discuss the terminology of HIV and AIDS, concepts like CD4 cell and viral load, signs and symptoms of HIV-related illness
8. Encourage to undergo regular medical check-up and to have appropriate lab tests (including PPD skin test for TB and pregnancy test, if indicated)
9. Provide educational materials, as appropriate

Disclosure in Health Care Settings

Disclosure of HIV infection to others is a serious and sensitive issue. Informed consent must be obtained for any disclosure. Health care workers have legal and ethical responsibilities to maintain the confidentiality of patient status and treatment.

Despite this, patients should be encouraged to disclose a diagnosis of HIV infection to all health care workers so that appropriate treatments can be provided.

However, most of the times, patients will not disclose as they do not feel safe. It is essential that all health care workers, including the paramedical staff, be oriented to the responsibility of maintaining confidentiality and managing clinic records appropriately.

Antiretroviral Therapy (ART)

Antiretroviral (ART) therapy refers to the use of pharmacologic agents that have specific inhibitory effects on HIV replication. These agents belong to four distinct classes of drugs: Nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and the fusion inhibitors (FIs). The current standard for formulating a highly active antiretroviral therapy (HAART) regimen recommends the use of either PIs or NNRTIs in combination with two nucleoside reverse transcriptase inhibitors.

Classification of Antiretroviral Drugs (Fig. 10.10)

1. Nucleoside reverse transcriptase inhibitors
2. Non-nucleoside reverse transcriptase inhibitors
3. Protease inhibitors
4. Fusion inhibitors.

Antiretroviral drugs	Class
Zidovudine (ZDV, AZT)	Nucleoside analogues
Lamivudine (3TC)	Nucleoside analogues
Stavudine (d4T)	Nucleoside analogues
Nevirapine (NVP)	Non-nucleosides
Delavirdine (DLV)	Non-nucleosides
Indinavir (IDV)	Protease inhibitors
Nelfinavir (NFV)	Protease inhibitors

Fig. 10.10: Antiretroviral drugs

Mode of Action

Nucleoside Reverse Transcriptase Inhibitors: Nucleoside reverse transcriptase inhibitors are faulty versions of building blocks that HIV needs to make more copies of itself. They act by incorporating themselves into the RNA of the virus (competing with natural nucleotides), thereby stopping the building process of transcription from RNA to DNA. The resulting DNA is incomplete and cannot create a new virus. Examples: zidovudine (ZDV), lamivudine (3TC), stavudine (d4T) and didanosine (ddL).

Non-nucleoside Reverse Transcriptase Inhibitors: They act by stopping HIV production by binding directly onto *reverse transcriptase* (non-competitively) and preventing the conversion of RNA to DNA. Examples: efavirenz (EFV), nevirapine (NVP), and delavirdine (DLV).

Protease Inhibitors: They act by binding to the viral *protease*, in this way preventing the correct cleavage of viral proteins. Thus, they prevent HIV from being successfully assembled and released from the infected cells. Examples: indinavir (IDV), nelfinavir (NFV), ritonavir (RTV), saquinavir (SQV), amprenavir (AMP).

Fusion Inhibitors: Fusion inhibitors work by blocking HIV entry into cells. Example: Enfuvirtide (T-20).

Indications for Antiretroviral Therapy

1. Symptomatic AIDS
2. Asymptomatic, AIDS - (CD4+ T cell count < 350 cells/$mm^3$and plasma HIV RNA any value)
3. Asymptomatic - (CD4+ T cell count > 350 cells/mm^3 and plasma HIV RNA > 100,000 copies/ml (RT-PCR or bDNA)
4. Asymptomatic - (CD4+ T cell count > 350 cells/mm^3 and plasma HIV RNA < 100,000 copies/ml (RT-PCR or bDNA)

Post-exposure Prophylaxis

Health Canada's Laboratory Center for Disease Control, in cooperation with the U.S. Centers for Disease Control and Prevention (CDC), issues recommendations on a variety of health concerns for the general population and for health care settings. One such recommendation, which has been modified relatively recently, is a protocol for post-exposure prophylaxis (PEP) of percutaneous injury with known HIV contaminated blood.

Healthcare personnel are at risk for occupational exposure to blood borne pathogens, including human immunodeficiency virus or HIV. Exposures occur through needle sticks or cuts from sharp instruments contaminated with an infected patients blood. Several clinical studies have demonstrated that HIV transmission

following occupational exposure can be significantly reduced by administration of antiretroviral agents or ARV. Therefore, post-exposure prophylaxis or PEP is an integral component of a complete program to prevent infection after an occupational exposure to blood.

Implementing PEP

PEP should be initiated as soon as possible, ideally within 2 hours and generally no later than 36 hours post-exposure. PEP provides a "window of opportunity" in limiting and preventing viral replication following exposure to blood. The prescribing provider should ensure that the health care worker or HCW has access to the full course of ARV drugs.

PEP Indications

PEP is indicated under the following circumstances:

1. Break in the skin by a sharp object that is contaminated with blood
2. Bite from a HIV infected patient with visible bleeding in the mouth that causes bleeding in the health care worker
3. Splash of blood to a mucosal surface (mouth, nose, or eyes)
4. A nonintact skin exposure to blood (e.g., dermatitis).

Risk of HIV Infection after Occupational Exposure among HCW

The average risk of HIV infection after percutaneous exposure is only 0.3%. The average risk of HIV infection after exposure of eye, nose, and mouth to HIV infected blood is estimated to be 0.1%. The average risk of HIV infection after exposure of non-intact skin to HIV-infected blood is estimated to be less than 0.1%.

According to CDC National Surveillance System for Healthcare Workers, June 1995 through August 2001, injuries occurred most frequently with small hollow bore needle (34%), followed by burs (13%), suture needles (11%), surgical scalpels (7%), scalers (6%), explorers (5%), and wires (4%); "other sharp objects" accounted for 20% (Fig. 10.11).

Injuries with other sharp objects, involved with large hollow bore needle (< 23-gauge) used

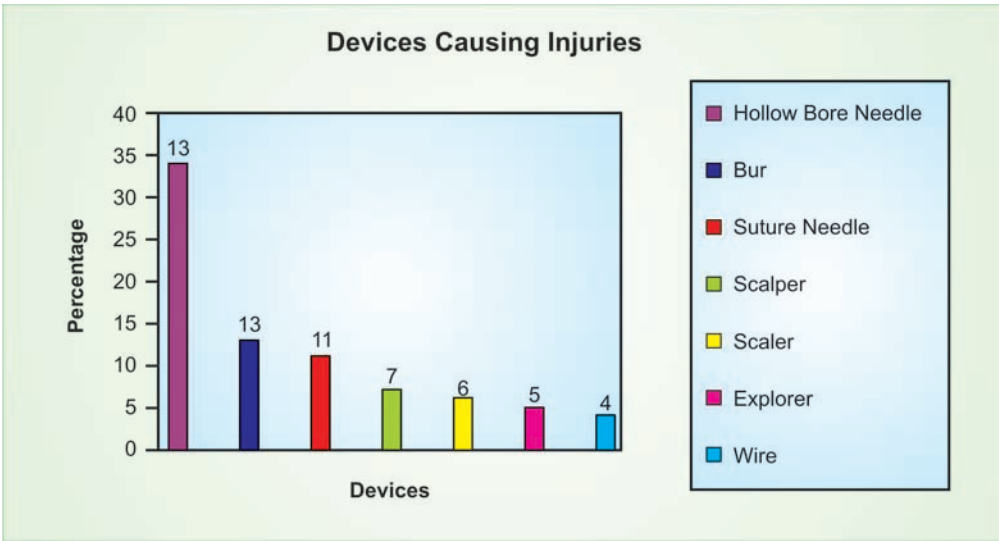

Fig. 10.11: Devices causing injuries

for blood collection, and another involved a needle used to deliver intravenous fluids.

After an occupational blood exposure, induce bleeding from the wound by squeezing the injury site and holding it under warm, running water, thoroughly wash the wound several times with an antimicrobial hand wash, primary closure of the wound, if necessary, should be performed, and report the exposure to the infection control department responsible for managing exposures.

Treatment of Exposure Site, Exposure Report and Evaluation of the Exposure

Each occupational blood exposure should be evaluated individually. This evaluation is based on the following:

1. The amount of blood involved
2. The details of the procedure being performed, including where and how the exposure occurred, type of device involved (e.g., small hollow bore needle), and when during its handling the exposure occurred
3. The type of exposure (e.g., percutaneous injury, contact with mucous membrane, contact with non-intact skin, bites resulting in blood exposure)
4. The infectious status of the source

Infection Status of the Source

The infection status of the source according to CDC is classified as:

1. **Class 1:** Asymptomatic HIV infection or patient has a known viral load of ≤ 1500 RNA copies/milliliter
2. **Class 2:** Symptomatic HIV infection, full blown AIDS or patient with known viral load of ≥ 1500 RNA copies/milliliter
3. **Unknown HIV Status:** The HIV status of the patient is unknown

PEP for Occupational Exposure

If PEP is indicated, it should start as soon as possible (within hours rather than days). The exposed person should be reevaluated within 72 hours and monitored for drug toxicity for at least two weeks. If the source patient is determined to be HIV-negative, PEP should be discontinued. Perform HIV-antibody testing for at least six months postexposure and perform HIV-antibody testing if illness with early "acute" phase occurs. Advice exposed persons to use precautions to prevent secondary transmission during the follow-up period. Because most occupational blood exposures do not result in transmission of HIV, the decision to recommend PEP must be based on the type of exposure, information about the infectious status of the source and side effects of PEP. When possible, the regimens should be implemented in consultation with persons who have expertise in antiretroviral treatment and HIV transmission.

According to CDC a basic regimen using two nucleoside reverse transcriptase inhibitors (NRTIs) is recommended if the source is Class 1. An expanded PEP regimen, which adds non-nucleoside reverse transcriptase inhibitors (NNRTIs) or a protease inhibitor (PIs) is recommended if the source is Class 2. The addition of a third drug should be considered for exposures that pose an increased risk for transmission.

In most cases, if the HIV status is unknown, no PEP is recommended. However, for source with HIV risk factors or in settings where they are likely to be HIV-positive, a basic two regimen using two nucleoside reverse transcriptase inhibitors is recommended.

1. **Class 1:** Zidovudine (ZDV) + lamivudine (3TC); lamivudine (3TC) + stavudine (d4T); stavudine (d4T) + didanosine (ddL).
2. **Class 2:** Zidovudine + lamivudine + indinavir or nelfinavir or efavirenz; lamivudine + stavudine + indinavir or nelfinavir or efavirenz.
3. **Unknown HIV status:** Zidovudine + lamivudine; lamivudine + stavudine; stavudine + didanosine.

The possible contributing factors which may result in failure of PEP include resistant HIV strain, high viral titer, delayed initiation of PEP, PEP of short duration, and decreased cellular immunity.

Avoiding occupational blood exposures is the primary way to prevent transmission of bloodborne pathogens in health care settings. Reducing injuries can be accomplished through appropriate use of barriers such as gown, gloves and eye protection, safely handling needles and other sharp instruments, and using devices with safety features as recommended by OSHA or Occupational Safety and Health Administration. In dentistry aspirating anesthetic syringes have been developed to incorporate safety features.

PEP for the Pregnant HCW

Before administering PEP to a pregnant woman, the clinician should discuss the potential benefits and risks to her and to the fetus (Fig. 10.12). Based on increasing clinical experience with HAART, PEP is indicated at any time during pregnancy when a significant exposure has occurred, despite possible risks to the women and the fetus. As HIV and ARV drugs may be found in the breast milk, breastfeeding should be avoided for 6 months after exposure to prevent HIV transmission and potential drug toxicities.

Drugs to avoid	Toxicity
Efavirenz	Neural tube defects
Combination of stavudine, and didanosine	Mitochondrial toxicity
Unboosted indinavir in the 2nd or 3rd trimester	Substantially lower antepartum indinavir plasma concentrations

Fig. 10.12: Drugs to avoid during pregnancy

Preventing Needlestick Injuries

Prevention of occupational infections with HIV includes:

1. Appropriate uses of barriers such as face mask, eye glasses, gloves, and drape.
2. Safely handling needles and other sharp objects
3. Using devices with safety features

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Chapter 11

Pregnancy and Dental Care

Pregnancy

INTRODUCTION

Management of a pregnant dental patient poses a unique challenge to the dentist, as he or she is solely responsible for providing safe and effective care to the mother and the developing fetus. There are number of anatomical and physiological, maternal changes during pregnancy. A sound knowledge of these changes will help the dental surgeon in careful management of the pregnant dental patient. Apart from these changes, various complications of pregnancy may complicate the dental treatment.

Terminology

1. **Nullipara:** Who has never completed a term of pregnancy
2. **Nulligravida:** Who has never become pregnant
3. **Primipara:** Who has delivered one viable child
4. **Primigravida:** Who is pregnant for the first time
5. **Multigravida:** Who has been previously pregnant
6. **Multipara:** Who has delivered two or more children
7. **Parturient:** Who is in labour
8. **Puerpera:** Who has just given birth

Fetal Development

First Trimester

The duration of the first trimester is first 12 weeks (84 days). The first 12 days from conception to implantation is the preimplantation period. Exposure to harmful drugs during preimplantation period can kill the embryo. From the 13th day, there is organogenesis and the fetus is susceptible to abortion and teratogenicity

Second Trimester

The duration of the second trimester is from 13 weeks to 28 weeks (112 days). It is the optimal trimester for dental care.

Third Trimester

The duration of the third trimester is from 29 weeks to 40 weeks (84 days). Dental care is not advisable during this period as the fetus is mature and there is an increased risk of supine hypotension, hypertension, and preeclampsia.

Anatomical and Physiological Changes during Pregnancy

Due to increasing demands of the fetus, there are various anatomical, physiological, endocrinal, and metabolic changes during pregnancy (Tables 11.1 to 11.4).

Table 11.1: Anatomical changes during pregnancy

Genital organs	*Anatomical changes*
Ovaries	Growth of corpus luteum
Fallopian tubes	Tubes are congested
Uterus	Increase in size increase in vascularity Increase in weight due to hypertrophy of the muscles Frequent changes in shape Position is altered and it lies on the bladder
Cervix	Hypertrophy and hyperplasia of the epithelium and connective tissue Hypertrophy and hyperplasia of the mucous glands Increase in vascularity Cervix becomes soft (Goodell's sign) Increased mucus secretion, which forms a mucosal plug that seals the cervical canal
Vagina	Increase in size The mucosa is violet in colour due to increase in vascularity (Jacqumier's sign) pH becomes acidic due to conversion of glycogen into lactic acid by *Lactobacillus acidophilus* because of high estrogen level
Breasts	Increase in size due to hypertrophy and hyperplasia of ducts and alveoli Hypertrophy and hyperplasia of the connective tissue stroma Increase in vascularity Increase in size of the nipples Pigmentation of the nipple and areola
Skin	Pigmentation of face (chloasma gravidarum or pregnancy mask) Pigmentation of the abdomen Striae gravidarum (stretch marks) Vascular spider Loss of hair Brittle nails

Table 11.2: Physiological changes during pregnancy

Systems	*Physiological changes*
Hematological changes	Due to increase in the blood volume and plasma volume there is hemodilution which results in fall of total hemoglobin concentration though there is an increase in total hemoglobin which indicates that hematological changes are only quantitative and not qualitative

Contd...

Contd...

	Increase in concentration of coagulation factors Increase in plasma fibrinogen level ESR is increased but has no significance
Cardiovascular system	Increased cardiac output due to increase in blood volume Blood pressure is normal in spite of increased cardiac output because of reduced peripheral resistance due to high level of progesterone Pulse rate is increased Heart is pushed upwards and outwards with a slight rotation to the left because of elevation of diaphragm due to enlarged fetus Palpitations due to displaced heart Apex beat is shifted to fourth intercostal space Systolic murmurs No hypertrophy or cardiac dilatation
Respiratory system	Breathlessness due to the action of progesterone on the respiratory centre and its increased sensitivity to arterial carbon dioxide
Digestive system	Decreased motility of gastrointestinal tract due to high level of progesterone Relaxed cardiac sphincter (sphincter of the esophagogastric junction) which leads to regurgitation of acid into esophagus causing heart burn
Excretory system	Increased renal blood flow Increased glomerular filtration rate Polyuria due to pressure applied on the bladder by the enlarged and displaced uterus
Nervous system	Mental irritability Sleeplessness Generalized neuritis due to vitamin B_1 (thiamine) deficiency Compression of lumbosacral trunk by the fetus may lead to paralysis of some leg muscles

Table 11.3: Endocrinal changes during pregnancy

Endocrine glands	*Endocrinal changes*
Pituitary gland	Hyperplasia of the pituitary gland Bitemporal hemianopia due to impingent on the optic chiasma by the hyperplastic pituitary gland Increased secretion of growth hormone Increased secretion of thyroid stimulating hormone Increased secretion of adrenocorticotrophic hormone Increased secretion of antidiuretic hormone Increased secretion of oxytocin
Thyroid gland	Hyperplasia of the thyroid gland Increased secretion of thyroxine Increased basal metabolic rate
Parathyroid gland	Hyperplasia of the parathyroid glands Increased secretion of parathyroid hormone

Contd...

Contd...

Adrenal cortex	Hyperplasia of the adrenal cortex especially zona fasiculata Increased secretion of glucocorticoids Absence of Cushing's syndrome with such plasma levels of glucocorticoids indicate that the tissue receptors are insensitive
Pancreas	Hyperplasia of the pancreas Increased secretion of glucagon Increased secretion of insulin (see anti-insulin factors)
Placenta	Progesterone and oestrogens (estriol, estradiol and estrone) Human chorionic gondaotrophin Human chorionic somatomammotrophin (placental lactogen) Human chorionic thyrotrophin Human chorionic corticotrophin TRH GnRH

Table 11.4: Metabolic changes during pregnancy

	Metabolic changes
Carbohydrate metabolism	Glycogenolysis Gluconeogenesis Maternal fasting hypoglycemia due to increased consumption of glucose by the fetus Postprandial hyperglycemia Altered insulin sensitivity due to tissue resistance, placental insulinase *(which degrades the insulin)*, human placental lactogen*(anti-insulin effect),* increased secretion of growth hormone, glucagons and glucocorticoids
Protein metabolism	Increased protein synthesis Positive nitrogen balance
Fat metabolism	Increased free fatty acid level because of breakdown of fats and increased absorption of fats Deposition of fats in the abdominal walls, breasts, hips and thighs
Iron metabolism	The total iron requirement during pregnancy is 1000 mg thus there is increased absorption of iron from the duodenum and jejunum which is then transported across the placenta to the fetus
Calcium metabolism	Due to increase in calcium demand by the fetus, there is an increase in absorption of calcium from the gut and kidneys due to the action of parathyroid hormone

Physiology of Female Sex Hormones

Oestrogens (estriol, estradiol and estrone) and progesterone are female sex hormones secreted by the ovaries, which play a major role in the life of women (Table 11.5). Progesterone is primarily a hormone of pregnancy and most of its actions in nongravid women are to prepare the female reproductive system for gestation.

Table 11.5: Physiology of female sex hormones		
Actions	*estradiol*	*progesterone*
Female reproductive tract	Enlargement of vagina Enlargement of external genitalia	
Secondary sexual characteristics	Widening of pelvic girdle Deposition of subcutaneous fat especially in the buttocks, thighs, and breasts	
Mammary gland	Growth of ducts	Growth of alveoli and lobules
Uterus.	Increases blood supply, which causes proliferation of uterine endometrium Increases contraction of myometrium Decreases the viscosity of mucus by increasing its water content	Increases blood supply to uterine endometrium Decreases contraction of myometrium Increases secretion of glands Increases the viscosity of mucus thereby forming mucus plug
Oviducts	Increases muscular contractions	Decreases muscular contractions Increases secretion of glands
Endothelium	Proliferation	Proliferation
Glycosaminoglycans	Reduce synthesis	Reduce synthesis

Physiology of Placental Hormones

During pregnancy, the placenta produces varieties of hormones of which steroid and protein hormones are important (Table 11.6). The placenta produces estriol rather than estradiol as secreted by the ovaries.

Table 11.6: Physiology of placental hormones	
Steroids	Progesterone Estrogens (estriol, estradiol and estrone)
Proteins	Human chorionic gondaotrophin Human chorionic somatomammotrophin (placental lactogen) Human chorionic thyrotrophin Human chorionic corticotrophin
Peptides	TRH GnRH

Progesterone Metabolism

Some hormones like testosterone become biologically active after metabolization, while progesterone becomes biologically inactive after metabolization. In healthy human gingiva, rate of progesterone metabolization is low, which may indicate the presence of high amounts of biologically active progesterone. However, in inflamed gingiva, the metabolism of progesterone is two to three times greater than in healthy gingiva. This may mean that there is a very low or negligible amount of biologically active progesterone in the inflamed tissue.

The reason as to why progesterone is not metabolized in an inflamed gingiva of pregnant patient is difficult to explain. However, progesterone may be responsible for the increased permeability of gingival vessels during

pregnancy. It is a well-known fact that progesterone concentrations in the maternal circulation are sufficient to cause immunosupression and that progesterone functions as an immunosuppressant in the placenta and other tissues during pregnancy. Thus, coexistence of these two important factors prevents acute-type of tissue reaction (which would keep the tissues clinically healthy) to plaque, which would otherwise keep the tissues healthy, but allows an increased chronic-type of tissue reaction, resulting in an exaggerated inflammatory clinical appearance.

Complications of Pregnancy

The dentist should be aware of the complications that complicate the pregnancy because any dental treatment may be looked upon as a causative factor for the complication especially abortion. Thus, a detailed case history prior to any dental procedure is of immense value as it rules out any complication.

Vomiting

Vomiting is a symptom, which may be related or unrelated to pregnancy.

Vomiting Related to Pregnancy

1. Simple vomiting
2. Hyperemesis gravidarum

Vomiting Unrelated to Pregnancy

1. Urinary tract infection
2. Hepatitis
3. Diabetic ketoacidodsis
4. Peptic ulcer

Simple vomiting is common during pregnancy and is a symptom. The pregnant patient complains of nausea and sickness on waking up in the morning. Hyperemesis gravidarum is a severe type of vomiting which has deleterious effects on the health of mother and incapacitates day-to-day life. A common feature in hyperemesis gravidarum is erosions of the palatal surfaces of upper anterior teeth.

Hemorrhage

The causes of hemorrhage in pregnancy may be related or unrelated to pregnancy.

Hemorrhage Related to Pregnancy

1. Miscarriage
2. Ectopic pregnancy
3. Hydatidiform mole

Hemorrhage Unrelated to Pregnancy

1. Polyps
2. Vascular erosions
3. Ruptured varicose veins
4. Malignancy

Anemia

Anemia is the most common hematological disorder that may occur during pregnancy. According to WHO, anemia during pregnancy is present when the hemoglobin concentration in the peripheral blood is $\leq$ to 11 gm/100 ml. The total iron requirement in pregnancy is approximately 1000 mg (placenta = 300 mg, fetus = 600 mg, and expanded red cell volume = 300 mg).

The iron present in the placenta and fetus is permanently lost along with iron present in expanded red cell volume, which is partially lost during delivery. Anemia in pregnancy may be due to the following reasons:

1. Preexisting anemic state
2. Decreased intake
3. Faulty diet
4. Multiple pregnancies
5. Increased demand for iron by the developing fetus
6. Polymorphism (polymorphism is a condition in pregnancy that tends to interfere with erythropoiesis by competing for the available raw materials such as iron, folic acid, vitamin B_{12}, and proteins.

Jaundice

If the serum bilirubin level exceeds 2 mg/100 ml (normal = 0.5-1.0 mg/100 ml) visible yellow staining of the tissues and mucous membranes. The causes of jaundice during pregnancy may be related or unrelated to pregnancy.

Jaundice Related to Pregnancy

1. Preeclampsia
2. Eclampsia
3. Hyperemesis gravidarum

Jaundice Unrelated to Pregnancy

1. Viral hepatitis
2. Gallstones (obstructive jaundice)
3. Mismatched blood transfusion (hemolytic jaundice)

Acute Abdominal Pain

Some amount of abdominal discomfort is common during pregnancy. However, severe abdominal pain and discomfort is indicative of underlying pathology. Few of the causes of acute abdominal pain are ectopic pregnancy, abortion, preterm labour, labour pains, hydatidiform mole, ruptured uterus, polyhydraminos, acute appendicitis, cystitis, and pyeliytis.

Asthma

During pregnancy, some amount of breathlessness is common due to the action of progesterone on the respiratory centre and its increased sensitivity to arterial carbon dioxide. Incidence of asthma is about 1% in all pregnant women. The course of asthma during pregnancy is unpredictable. It may improve, deteriorate or may remain unchanged.

Gestational Diabetes Mellitus

Gestational diabetes is present in the late second and during third trimester of pregnancy. Screening for gestational diabetes mellitus is between 24 and 28 weeks. However, after parturition the blood glucose levels return to normal. The various mechanisms that lead to gestational diabetes are:

1. Increased absorption of glucose from alimentary tract
2. Inability of insulin to convert glucose into glycogen
3. Impaired tubular reabsorption of glucose which leads to glycosuria

Hypertension

Hypertension is one of the common complications in pregnancy. It is a sign of underlying pathology, which may be preexisting or appearing for the first time during pregnancy. The causes of hypertension in pregnancy may be related or unrelated to pregnancy.

Hypertension Related to Pregnancy

1. Preeclampsia
2. Eclampsia

Preeclampsia: Preeclampsia is a multisystem disorder of unknown etiology, induced during pregnancy after the 20th week and characterized by development of hypertension to the extent of 140/90 mmHg or more with proteinuria.

Eclampsia: In Greek, eclampsia means *"like a flash of lightning."* Eclampsia may occur quite abruptly, without any warning manifestations. Usually features of severe preeclampsia precede eclampsia.

Hypertension Unrelated To Pregnancy

1. Thyrotoxicosis
2. Coarcation of aorta
3. Pheochromocytoma
4. Essential hypertension
5. Renovascular hypertension
6. Systemic lupus erythematosus

Supine Hypotension

During pregnancy, the gravid uterus compresses the inferior vena cava when the patient is in a supine position, which results in opening of the collateral circulation by means of paravertebral and azygos veins. In 10% of the cases, the collateral circulation fails to open up which results in supine hypotension, tachycardia, and syncope. By turning the patient to a lateral position, the normal blood pressure is restored.

ORAL MANIFESTATIONS OF PREGNANCY

The oral manifestations of pregnancy are:

1. Pregnancy tumor (pregnancy granuloma, epulis gravidarum)
2. Pregnancy gingivitis (gingivitis gravidarum)
3. Erosions of hard tissues

Pregnancy Tumor

Pyogenic granuloma is a benign inflammatory lesion composed of proliferating capillaries and endothelial cells (exuberant granulation tissue) in a lobular pattern, accompanied by mixed inflammatory cell infiltrate. Pyogenic granuloma is well-known in dermatology and the term "lobular capillary hemagioma" is gaining favor in the dermatologic literature. Pyogenic granuloma commonly occurs in the gingiva but may be present on the tongue, lips, or buccal mucosa.

Pyogenic granuloma of the gingiva is "pregnancy tumor." Pregnancy tumor is a clinical term used to describe a red or reddish purple, often nodular, and/or ulcerated localized tumor that bleeds easily. Pregnancy tumor is a clinical diagnosis for a red swelling, usually an epulis, in pregnant women. It is single but may be multiple and may grow rapidly. The clinical onset of pregnancy tumor is around the second or third trimester. Histologically pregnancy tumor is identical to pyogenic granuloma. Recurrence of the excised lesion is common during pregnancy. Partial or complete regression of the lesion is common after childbirth.

Pathogenesis

There is an increased frequency of pregnancy tumor during pregnancy. The three major hormones produced by the placenta are progesterone, oestrogens (estriol, estradiol and estrone), and human chorionic gondaotrophin. Human chorionic gondaotrophin is in large amounts during the first 10 weeks of pregnancy, after which levels fall dramatically. Therefore, it seems unlikely that this hormone plays a role in the pathogenesis of pregnancy tumor. On the other hand, the concentrations of progesterone and oestrogens rise steadily until childbirth. By the end of 40th week of pregnancy, the oestrogen production is 100 times more than the oestrogen levels of the nonpregnant female. This indicates that there is an increased incidence of pregnancy tumor as pregnancy progresses.

The gingiva is subjected to higher levels of these hormones not only through the bloodstream but also from saliva. This additive effect explains why so many pregnancy tumors occur in the oral cavity. Many authors stress the importance of some form of chronic low-grade irritation (plaque, calculus, irregular dental restorations) as the inciting factor, with the response enhanced by female sex hormones (Fig.11.1). For a lesion to respond to oestrogen and progesterone, the vascular endothelial cells must exhibit receptors for these hormones. However, very low concentrations of estrogen and progesterone receptors are present in gingival vessels. It is a well-known fact that oestrogen induces neovascularity of the endometrium in the proliferative phase of the menstrual cycle.

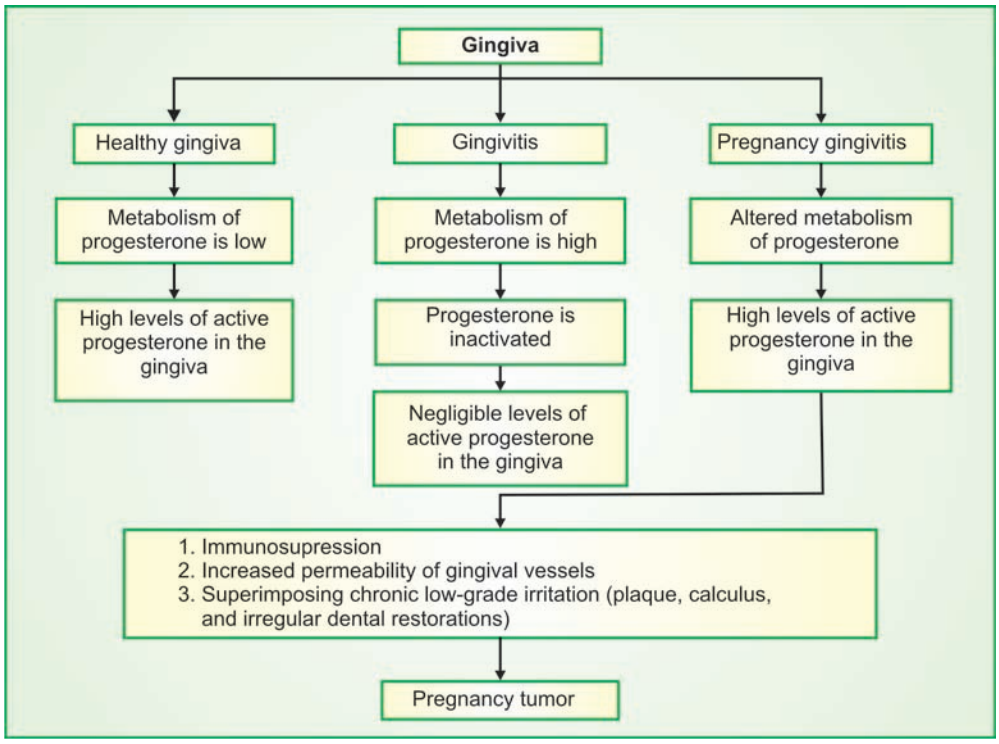

Fig. 11.1: Pathogenesis of pregnancy tumor

Treatment Protocol for Pregnancy Tumor

Surgical excision is not required for lesions that do not cause significant functional or esthetic problems as they may recur. However, surgical excision is required for lesions, which do not resolve after pregnancy.

Pregnancy Gingivitis

The gingiva in pregnancy is oedematous and characterized by marked tendency towards bleeding and histologically has no specific feature distinguishing it from normally inflamed gingiva. The oedematous appearance of the gingiva is due to increased levels of estradiol (E_2) and progesterone as they reduce the synthesis of glycosaminoglycans, which are hydrophilic. Pregnancy gingivitis is more common at the incisor region than the premolar and molar region.

Pharmacological Considerations

Administration of drugs to pregnant patients is of significant concern because of the teratogenic, toxic, or otherwise harmful effects of drugs on the developing fetus. The placenta does not strictly constitute a barrier and any drug can cross

it to a greater or lesser extent. The embryo is one of the most dynamic biological systems and in contrast, to adults, drug effects are often irreversible.

Teratogenicity refers to capacity of a drug to cause fetal abnormalities when administered to the pregnant mother. The teratogens disturb organogenesis in the developing embryo so that defects in one or more structures are produced. If the defects are incompatible with life, fetal death, or spontaneous abortion ensues and if they are less severe, the result is a malformed child. The teratogenic potential of drugs became evident during 1960-1962 when women to relieve morning sickness used an extremely safe sedative—hypnotic drug by the name thalidomide. This was followed by thalidomide disaster characterized by infants born with phocomelia, or "seal limb" malformation of the arms and legs. Other defects produced by thalidomide were absence of external ears, cranial nerve dysfunction, and anorectal stenosis. Surprisingly thalidomide has made a comeback as a treatment option for Behcet's syndrome, and recurrent aphthous ulceration in patients infected with HIV.

The clinician should understand the interaction between drugs and pregnancy in order to avoid disastrous consequences. Although pregnant women do not differ qualitatively from the nongravid women in their response to drugs, certain quantitative differences do occur because of physiological changes during pregnancy. These physiological changes and the consequent alterations in pharmacokinetics lead to changes in drug absorption, distribution, excretion, and metabolism.

Drug Absorption

Because of high levels of progesterone the gastrointestinal motility is decreased which results in slower drug absorption. Thus, in order to obtain a quick response parenteral drug administration is preferred.

Drug Distribution

The albumin binding capacity of drugs is decreased during pregnancy due to hemodilution as a result; freer drug is available for placental transfer.

Drug Excretion

During pregnancy, the renal blood flow increases by 25-50% and the glomerular filtration rate by 50%. Therefore, drugs are rapidly eliminated which depend on the kidney.

Drug Metabolism

The level of hepatic drug metabolizing enzymes is high probably due to high levels of progesterone. This leads to rapid metabolic degradation of lipid soluble drugs.

FDA Pregnancy Risk Categories

The Food and Drug Administration (FDA) has classified drugs with respect to their toxic potential during pregnancy (Table 11.7). Drugs in categories D, X, and in some cases C, may pose similar risk.

Table 11.7: FDA pregnancy risk categories	
Category	*Definition*
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy and there is no evidence of risk in later trimesters.
B	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy and there is no evidence of risk in later trimesters, but animal reproduction studies have shown an adverse effect on the fetus or human studies are lacking, but animal studies have failed to demonstrate a risk to the fetus.
C	No adequate and well-controlled studies have been performed in pregnant women, but animal reproduction studies are lacking or have shown an adverse effect on the fetus. Potential benefit may warrant use of the drug in pregnant women despite potential risk.
D	Positive evidence exists of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans. Potential benefit may warrant use of the drug in pregnant women despite potential risk.
X	Studies in animals and humans have demonstrated fetal abnormalities, and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the potential risk of the drug in pregnant women clearly outweighs the potential benefit.

Drug Considerations in Pregnant Patient

Maternal medication	Category first trimester	Category second trimester	*Category third trimester*
Local Anesthetics			
Lignocaine	B	B	B
Mepivacaine	C	C	C
Nonopioid Analgesics			
Aspirin	C	C	D
Celecoxib	C	C	D
Diclofenac sodium	B	B	D
Ibuprofen	B	B	D
Mefenamic acid	C	C	D
Nimesulide	X	X	X
Paracetamol	B	B	B
Valdecoxib	C	C	C
Antimicrobials			
Acyclovir	B	B	B
Amoxycillin	B	B	B
Ampicillin	B	B	B
Amphotericin B	B	B	B
Cefazolin	B	B	B
Cefotaxime	B	B	B

Contd...

Contd...

Cefalexin	B	B	B
Chloramphenicol	C	C	C
Clindamycin	B	B	B
Clotrimazole	B	B	B
Cloxacillin	B	B	B
Co-trimoxazole	C	C	D
Erythromycin	B	B	B
Fluconazole	C	C	C
Ketoconazole	C	C	C
Metronidazole	B	B	B
Nystatin	C	C	C
Ofloxacin	D	C	C
Streptomycin	D	D	D
Tetracycline	D	D	D
Corticosteroids			
Betamethasone	D	C	C
Dexamethasone	D	C	C
Prednisolone	D	C	C
Triamcinolone	D	C	C
Sedatives			
Alprazolam	D	D	D
Clonazepam	D	D	D
Diazepam	D	D	D
Lorazepam	D	D	D
Antiallergic			
Chlorpheniramine maleate	B	B	B
Antiepileptic			
Carbamazepine	*D*	*D*	D

Dental Management

The main objective is to protect the developing fetus and the expecting mother and the important points to consider in management of a pregnant dental patient are:

1. A written consent from gynecologist is required because any dental treatment may be looked upon as a causative factor for abortion
2. A detailed case history should be undertaken, which should include history of previous pregnancy or pregnancies and complications
3. The approach of the dentist in management of a pregnant dental patient should be conservative
4. The importance of oral hygiene must be stressed and dietary instructions given

5. Avoid elective dental care in first and third trimester
6. Only emergency procedures are accomplished during the first trimester and late third trimester
7. The optimal trimester for dental care is second trimester
8. The duration of the treatment procedure should be short
9. At the beginning of second and third trimester, oral prophylaxsis should be undertaken
10. In order to prevent supine hypotension during third trimester the patient should be in a sitting position rather than lying down
11. Elective radiography is contraindicated but when taken lead apron is mandatory

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Chapter 12

Systemic Diseases and Dental Care

I. ORAL HEALTH AND HEART HEALTH

BASIC CARDIOLOGY

HEART STRUCTURE

External Structure of the Heart

The heart is a roughly cone-shaped hollow muscular organ, measures about 10 cm long and about the size of the owner's fist. Its approximate weight is 225 g in women and 310 g in men.

The heart lies obliquely in the thoracic cavity in the mediastinum between the lungs, is rotated to the left than the right, and presents a base above, and apex below.

The apex is about 9 cm to the left of the midline at the level of the fifth intercostal space, i.e., a little below the nipple and slightly near the midline. The base extends to the level of the second rib. The various organs associated with the heart are:

1. **Superiorly:** The great blood vessels (superior vena cava, arch of aorta, pulmonary artery, and pulmonary veins)
2. **Inferiorly:** The diaphragm
3. **Anteriorly:** The sternum, ribs, and intercostal muscles
4. **Posteriorly:** The trachea, right and left bronchus, esophagus, descending aorta, and inferior vena cava
5. **Laterally:** The lungs, with the left lung overlapping the left side of the heart

The heart is composed of three layers of tissue: pericardium, myocardium, and endocardium.

Pericardium

The pericardium is made up of two sacs the outer fibrous and the inner serous. The outer fibrous sac is continuous with the tunica adventitia of the great blood vessels above and is adherent to the diaphragm below. Its inelastic and fibrous nature prevents the overexpansion of the heart.

The inner serous sac is composed of two layers, an outer parietal pericardium and an inner visceral pericardium or epicardium. The outer parietal pericardium lines the outer fibrous sac. The inner visceral pericardium lines the myocardium.

The space between the outer parietal pericardium and inner visceral pericardium is known as pericardial space. The pericardial space is lined by flattened epithelial cells that secrete the serous pericardial fluid. The serous pericardial fluid allows smooth movement between outer parietal pericardium and inner visceral pericardium when the heart beats. Normally the outer parietal pericardium and inner visceral pericardium are in close association with only thin film of serous pericardial fluid.

Myocardium

The myocardium is composed of specialized muscle found only in heart. Unlike skeletal muscle it is not under voluntary control. Each cardiac muscle cell (fiber) has a nucleus and one or more branches. The ends of each cardiac muscle cell are in very close contact with the ends of the adjacent cardiac muscle cell *via* intercalated discs.

The intercalated discs are actually cell membranes that separate individual cardiac muscle cells from one another and are seen as dark lines under the microscope. Because of connectivity between the individual cardiac muscle cells, each cell does not need to have separate nerve innervation. Thus, when an impulse is initiated it spreads from cell to cell causing contraction of the myocardium.

The myocardium is thickest at the apex especially the left ventricle and thins out towards the base. This reflects the amount of work each chamber contributes to the pumping of blood.

Endocardium

The endocardium lines the myocardium and the heart valves. It is a thin, smooth, shining membrane, which permits smooth flow of blood inside the heart. It consists of flattened epithelial cells, which are continuous with the endothelium that lines the great blood vessels.

Internal Structure of the Heart (Fig.12.1)

Internally the heart is divided into right and left side by a septum consisting of myocardium lined by endocardium. Each side is divided by an atrioventricular valve into an upper chamber, the atrium and a lower chamber, the ventricle. The atrioventricular valves consist of myocardium lined by endocardium. The right atrioventricular valve (tricuspid valve) has three flaps or cusps and the left atrioventricular valve (mitral valve) has two flaps or cusps.

The valves between the atria and ventricles open and close passively according to pressure changes within the chambers. They open when

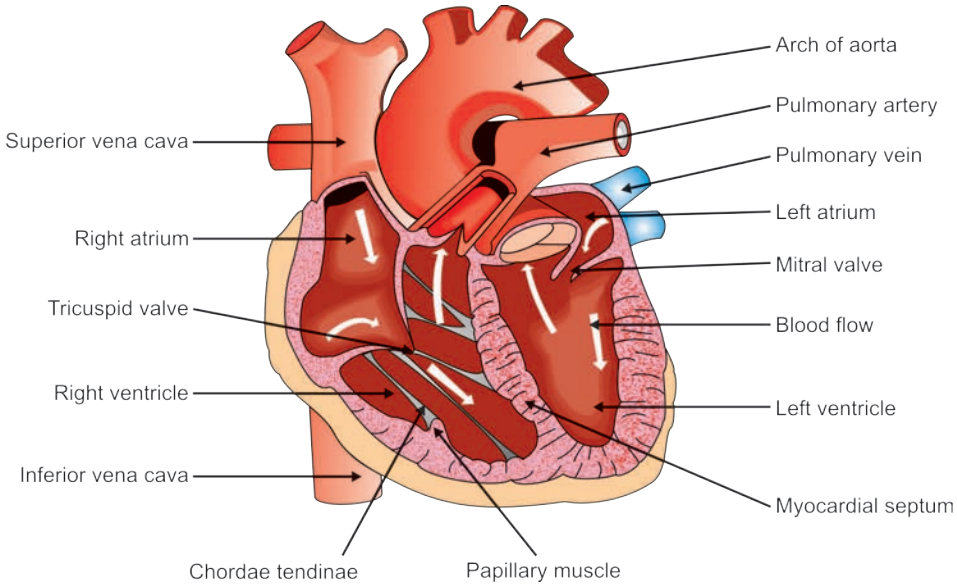

Fig. 12.1: Internal structure of heart

the pressure in the atria is greater than that in ventricles (atrial systole) and close when pressure in the ventricles is greater than that in atria (ventricular systole). The valves are prevented from opening upwards into the atria by tendinous cords, called chordae tendineae. The chordae tendineae extend from the inferior surface of the cusps to little projections of the myocardium lined by endocardium, called papillary muscles.

Flow of Blood through the Heart

The two largest veins of the body, the superior and inferior vena cava empty the blood into the right atrium. This blood passes *via* the right atrioventricular valve into the right ventricle from where it is pumped into the pulmonary artery (the only artery in the body that carries deoxygenated blood). The opening of the pulmonary artery is guarded by pulmonary valve, formed by three semilunar cusps. The pulmonary valve prevents the backward flow of blood into the right ventricle when the ventricles relax.

After leaving the heart, the pulmonary artery divides into right and left branches, which carry the deoxygenated blood to the lungs where carbon dioxide is excreted and oxygen is absorbed. Two pulmonary veins from each lung carry oxygenated blood back to the left atrium. The oxygenated blood passes *via* the left atrioventricular valve into the left ventricle from where it is pumped into the aorta (first artery of circulation). The opening of the aorta is guarded by aortic valve, formed by three semilunar cusps. The aortic valve prevents the backward flow of the blood into the left ventricle when the ventricle relaxes. It should be noted that the right and left atria contract at the same time and this is followed by the simultaneous contraction of right and left ventricles.

Blood Supply to the Heart

The heart is supplied with arterial blood by the right and left coronary arteries, which branch, from the aorta immediately distal to the aortic valve. The right and left coronary arteries receive about 5% of the blood pumped from the heart. The right coronary artery travels in the coronary sulcus to reach the posterior surface of the heart where it anastomoses with the circumflex left coronary artery. Early in its course, it gives off the SA node artery, AV node artery, marginal branch, and a posterior descending branch in the interventricular groove, which anastomoses with the anterior descending left coronary artery. The left coronary artery divides into circumflex left coronary artery, and anterior descending left coronary artery in the interventricular groove. The right and left coronary arteries traverse (cross) the heart and form a vast network of capillaries.

Venous Drainage of the Heart

The deoxygenated blood is collected by the oblique vein of the left atrium, small cardiac vein, middle cardiac vein, and the great cardiac vein. These veins join to form the coronary sinus, which opens into the right atrium between the opening of inferior vena cava and the right atrioventricular valve. A semicircular valve guards the opening of coronary sinus.

Conducting System of the Heart

The conducting system of the heart is composed of specialized neuromuscular tissue in the myocardium, which initiates and conducts impulses causing coordinated (operating as a unit) and synchronized (operating at the same time) contraction of the myocardium.

The conducting system of the heart is not dependent on the innervation from the brain.

However, the conducting system can be stimulated or depressed by nerve impulses initiated in the brain and by the circulating chemicals and hormones.

Sinoatrial Node (SA Node)

The sinoatrial node is a small, flattened, ellipsoid mass of specialized neuromuscular tissue that is situated in the posterosuperior lateral wall of the right atrium immediately below and slightly lateral to the opening of the superior vena cava. The SA node is the "pacemaker" of the heart because it initiates the cardiac muscle contraction and determines the heart rate.

Atrioventricular Node (AV node)

Three internodal fibers (anterior internodal fibers of Bachman, middle internodal fibers of Wenckebach, and posterior internodal fibers Thorel) conduct the impulses from SA node to the AV node (i.e., they converge towards the AV node and interdigitate with fibers of AV node). The AV node is a small, oval or elliptical mass of specialized neuromuscular tissue that is situated in the wall of interatrial septum near the atrioventricular valves in the triangle of Koch. Normally the AV node is stimulated by the impulses originating in the SA node. However, the AV node is capable of initiating impulses that cause contraction but at a slower rate than the SA node.

Atrioventricular Bundle (AV bundle or bundle of His)

The AV bundle is a mass of specialized neuromuscular tissue that originates from the AV. At the upper end of interventricular septum the AV bundle divides into right and left bundle branches. These bundle branches run on either side of the interventricular septum and give of fine fibers called the Purkinje fibers within the ventricular myocardium. The AV bundle, bundle branches, and Purkinje fibers conduct impulses from the AV node to the apex of the myocardium. From the apex of the myocardium, the wave of ventricular contraction begins, which sweeps upwards and outwards, pumping blood into the pulmonary artery and the aorta.

Innervation to the Heart

The heart is innervated by the sympathetic and parasympathetic nerves.

Sympathetic

The cell bodies of the preganglionic sympathetic nerve fibers are located in the lateral column of grey matter in the spinal cord between the levels of T1 and L3 and are known as spinal sympathetic centers. The spinal sympathetic centers are not independent centers. They are under the control of vasomotor center present in the ventrolateral medulla. The vasomotor center is controlled by the higher centers (cerebral cortex and hypothalamus), nucleus of the tractus solitarus, and is sensitive to oxygen tension and pH of the arterial blood. The preganglionic sympathetic nerve fibers leave the spinal cord *via* the anterior root and terminate in the lateral chain of sympathetic ganglia. The preganglionic sympathetic nerve fibers release the neurotransmitter acetylcholine.

The postganglionic sympathetic nerve fibers have their cell bodies in the lateral chain of sympathetic ganglia. The postganglionic sympathetic nerve fibers release the neurotransmitter noradrenaline and innervate the tissues or the target organs e.g., salivary glands, heart, arterioles, capillaries, veins, coronary arteries, and skeletal blood vessels. The postganglionic sympathetic nerve fibers raise the total peripheral resistance and blood pressure by vasoconstriction of the arterioles, capillaries, and veins. Under normal conditions the

postganglionic sympathetic nerve fibers exert a continuous discharge on the arterioles, capillaries, and veins all over the body and maintain a partial state of vasoconstriction, called vasomotor tone. However, the postganglionic sympathetic nerve fibers that innervate the coronary arteries and blood vessels supplying the skeletal muscle cause vasodilatation.

The cell bodies of the preganglionic sympathetic nerve fibers that innervate the heart are located in the lateral column of grey matter in the spinal cord between the levels of T1 and T4. The postganglionic sympathetic nerve fibers innervate the SA node, AV node, and the myocardium of atria and ventricles. Stimulation of postganglionic sympathetic nerve fibers leads to increase in heart rate (positive chronotropic effect), and increase in force of contraction (positive ionotropic effect).

Parasympathetic

The parasympathetic nerve cell bodies of the vagus nerve (visceral motor component of vagus nerve) are located in the dorsal motor nucleus of the vagus. The parasympathetic nerve cell bodies are influenced by inputs from the hypothalamus, the olfactory system, the reticular formation, and the nucleus of the tractus solitarius. The dorsal motor nucleus of the vagus is located in the floor of the fourth ventricle (vagal trigone) and in the central grey matter of the medulla. Preganglionic parasympathetic nerve fibers arise from dorsal motor nucleus of the vagus traverse the spinal nucleus of the trigeminal nerve and emerge from the lateral surface of the medulla, and travel in the vagus nerve. Within the thorax, the preganglionic parasympathetic nerve fibers of vagus nerve innervate the heart through the right and left cardiac branches.

The preganglionic parasympathetic nerve fibers innervate mainly the SA node, AV node, and the myocardium of atria. Stimulation of preganglionic parasympathetic nerve fibers leads to decrease in heart rate (negative chronotropic effect), and decrease in force of contraction (negative ionotropic effect). The preganglionic parasympathetic nerve fibers that innervate the heart exert a continuous discharge which keeps the heart rate within normal limits (vagal tone) even at rest. The heart rate of healthy adults at rest is usually between 60-75 beats/minute. In fetus, the heart rate is about 140 beats/minute. After delivery the heart rate of the newborn decreases, but is on the higher side in comparison to adults. The adult heart rate is achieved at the age of 18 years. The heart rate decreases in middle age and increases again in old age.

Blood Pressure

Definition

Arterial blood pressure is the lateral pressure exerted by the contained column of blood on the wall of arteries (Fig.12.2). The pressure is exerted when the blood flows through the arterioles. The two main factors that determine the blood pressure are cardiac output and peripheral resistance. Two terms that express arterial blood pressure are:

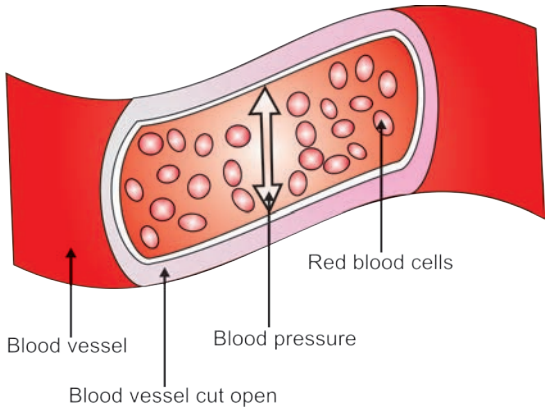

Fig. 12.2: Blood pressure

1. **Systolic pressure:** Systolic pressure is the maximum pressure exerted in the arteries during the systole of heart
2. **Diastolic pressure:** Diastolic pressure is the minimum pressure in the arteries during the diastole of the heart

Regulation of Normal Blood Pressure

The arterial blood pressure varies even under normal physiological conditions. However, immediately it is brought back to normal level because of well-organized regulatory mechanisms. The various regulatory mechanisms are:

1. Neural regulation or short-term
2. Renal regulation or long-term

Neural Regulation or Short-term

The baroreceptors are stretch receptors present in the walls of the atria, pulmonary veins, wall of the left ventricle, wall of the aortic arch, and carotid sinuses. The carotid sinuses are slight dilatations present in the wall of each internal carotid artery slightly above the common carotid artery bifurcation. When there is a rise in the arterial blood pressure, the nerve endings of the peripheral processes of the glossopharyngeal nerve (Hering's nerve) and vagus nerve present in the baroreceptors are stimulated and the impulses are transmitted *via* these peripheral processes whose cell bodies are located in the inferior ganglion.

From the inferior ganglion, the impulses are transmitted *via* the central processes, which enter the medulla and descend in the tractus solitarius to enter the caudal part of the nucleus of the tractus solitarius. The nucleus of the tractus solitarius sends inhibitory impulses to the vasomotor center (C1) *via* the inhibitory interneurons. The vasomotor center in turn sends inhibitory impulses to the spinal sympathetic center *via* the bulbospinal pathway. Inhibition of the spinal sympathetic center results in vasodilatation of the arterioles and veins, decrease in heart rate, and decrease in blood pressure.

Renal Regulation or Long-term

The renin-angiotensin system (Fig.12.3) plays an important role in the regulation of arterial blood pressure. Renin is small protein enzyme synthesized and stored in an inactive form called prorenin in the juxtaglomerular cells (JG cells).

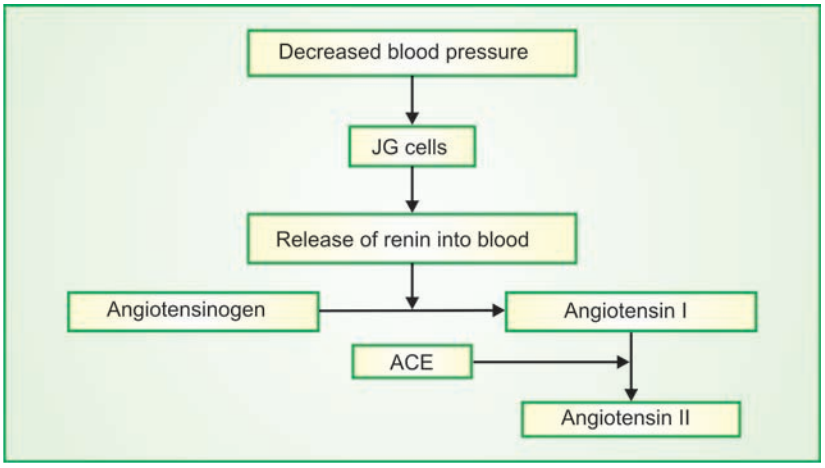

Fig. 12.3: The renin-angiotensin mechanism

The JG cells are modified smooth muscle cells located in the wall of afferent arteriole immediately proximal to the glomerulus. When there is a fall in arterial blood pressure, the prorenin molecules split and the JG cells release renin.

The renin enters the renal blood and then passes out of the kidneys to circulate throughout the body. Renin is not a vasoactive substance but a protein enzyme that acts on circulating α_2-globulin, called angiotensinogen, or renin substrate to release angiotensin I. The

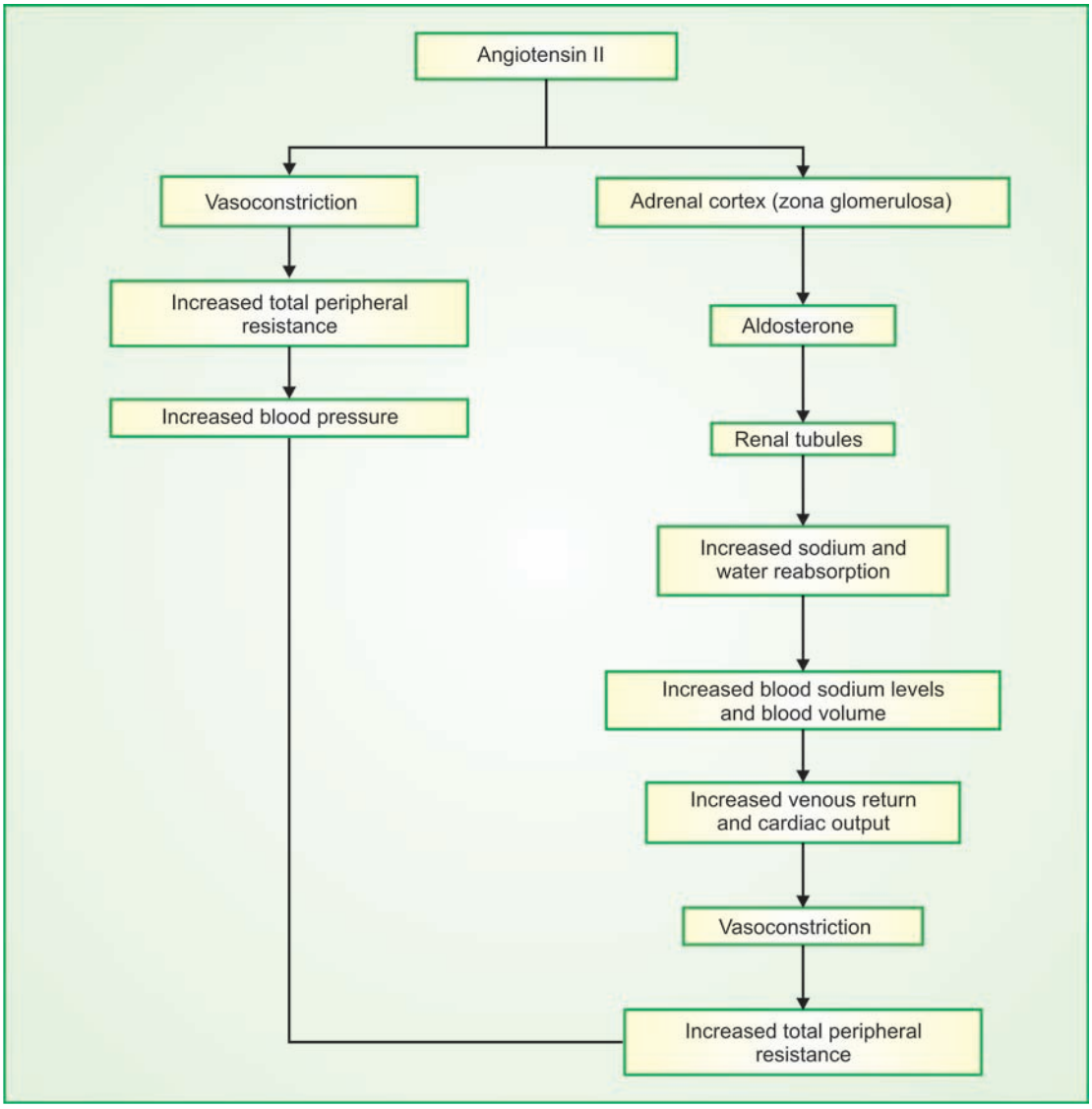

Fig. 12.4: The effects of Angiotensin II

angiotensin I has mild vasoconstrictor properties but it is not effective to cause any functional changes in the circulation. Within a few seconds after the formation of the angiotensin I, two additional amino acids are split from the angiotensin I to form 8-amino acid peptide angiotensin II.

This conversion occurs entirely in the lungs and is catalyzed by angiotensin converting enzyme (ACE) that is present in the endothelium of the lung blood vessels. Angiotensin II persists in the blood for 1 to 2 minutes because multiple blood and tissue enzymes collectively called angiotensinase rapidly metabolize it. During its presence in the blood angiotensin II has two effects (Fig.12.4) that can elevate the arterial blood pressure. The two effects are:

1. **Vasoconstriction:** Vasoconstriction of arterioles increases the total peripheral resistance thereby increasing the arterial blood pressure. It also causes vasoconstriction of veins including the splanchnic veins thereby increasing the venous return to the heart.
2. **Direct action on the kidneys:** The angiotensin II stimulates zona glomerulosa of the adrenal glands to secrete aldosterone. The aldosterone increases sodium and water reabsorption from the distal convoluted tubules and collecting tubules. Sodium and water reabsorption increases the blood sodium levels and blood volume, which in turn increases the venous return, and the cardiac output. Thereby increasing the blood pressure.

HYPERTENSION

Persistent increase in systemic arterial pressure is known as hypertension. Clinically when the systolic blood pressure rises above 140 mm Hg and diastolic pressure rises above 90 mm Hg, it is considered as hypertension. If there is increase only in systolic blood pressure, it is called systolic hypertension.

Depending on the cause hypertension may be described as essential (primary or idiopathic) or secondary (secondary to other disease). However, irrespective of the cause, hypertension commonly affects the kidneys.

Types of Hypertension

Essential

Essential hypertension is a complex multifactorial disorder the cause of which is unknown (idiopathic). Various environmental factors (heavy consumption of salt, sedentary life style, obesity, excessive intake of alcohol, and cigarette smoking) affect the variables (cardiac output and peripheral resistance) that control blood pressure in the genetically predisposed patients. Essential hypertension accounts for 85-90% of all cases and is subdivided as benign and malignant according to the rate at which the disease progresses.

1. **Benign (chronic) hypertension:** In benign hypertension, the blood pressure rises slowly over many years and is compatible with long life, unless there are complications like myocardial infarction, cerebrovascular accident, or congestive cardiac failure. Occasionally the rate of progress of blood pressure increases and hypertension becomes malignant.
2. **Malignant (accelerated) hypertension:** In malignant hypertension, the blood pressure continues to rise rapidly. Diastolic pressure in excess of 120 mm Hg is common. The effects are serious and quickly become apparent, e.g., retinal hemorrhages, papilledema (edema around the optic disc),

encephalopathy (cerebral edema), and renal failure. Malignant hypertension, if left untreated, leads to death within 1 to 2 years.

Mechanism of Essential Hypertension

Essential hypertension occurs when the environmental factors affect the variables that control blood pressure in the genetically predisposed patients. The various genetic factors are decreased renal sodium excretion and functional vasoconstriction (Fig.12.5).

1. **Decreased renal sodium excretion:** Decreased renal sodium excretion leads to increase in the ECF and blood volume, increase in the venous return, increase in the cardiac output and vasoconstriction, thereby elevating the blood pressure
2. **Functional vasoconstriction:** Functional vasoconstriction increases the peripheral resistance and blood pressure. Moreover, chronic or repeated vasoconstriction causes thickening of arterioles (resistance vessels) and subsequent increase in peripheral resistance and blood pressure

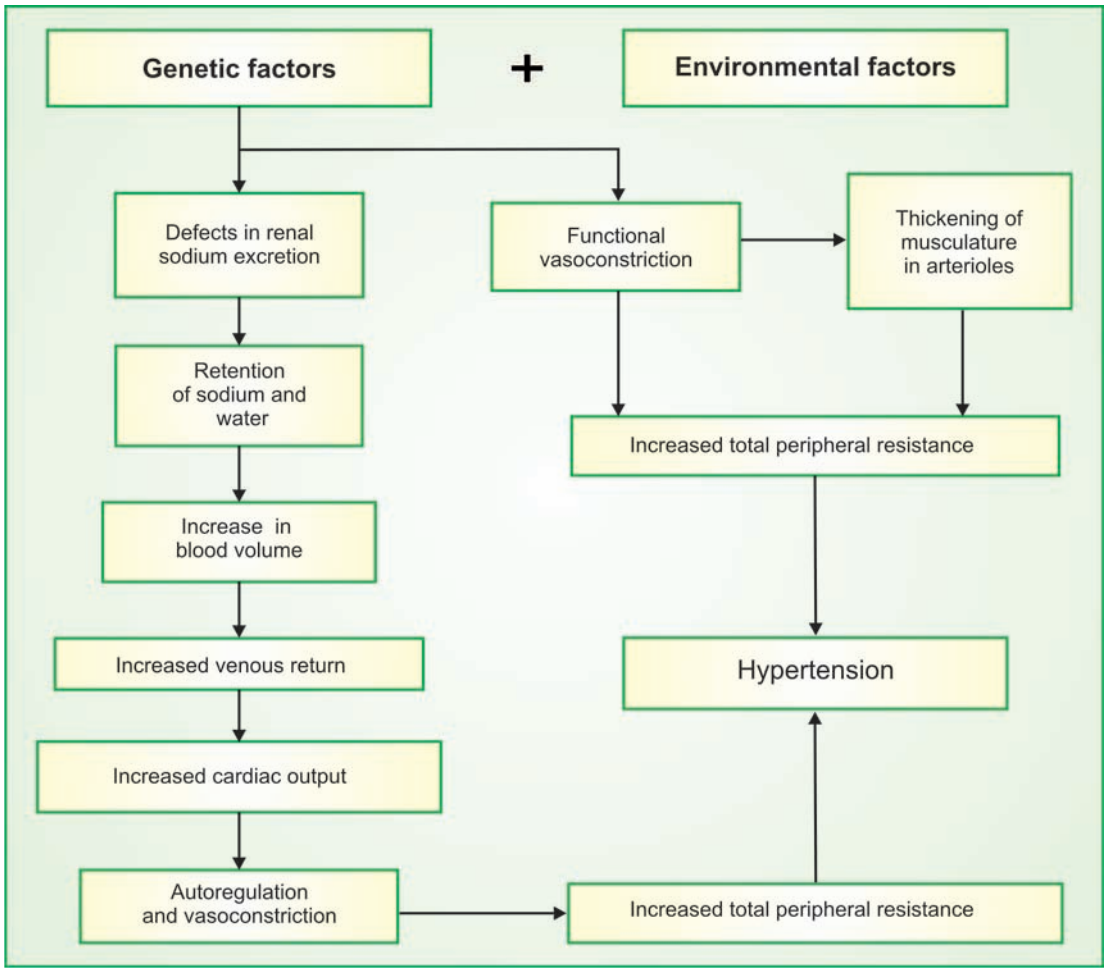

Fig. 12.5: Mechanism of essential hyertension

Secondary

Secondary hypertension is secondary to other diseases and accounts for 10-15% of all cases. The various causes of secondary hypertension are given in Table 12.1

Complications of Hypertension

The effects of long standing and progressively rising blood pressure are serious (Table 12.2).

Treatment

The management of hypertension includes modification of lifestyle and drug therapy (Table 12.3).

Table 12.2: Complication of hypertension

Systems	*Complications*
Heart	Right ventricular hypertrophy Left ventricular hypertrophy Cardiac failure Ischemic heart disease
Blood vessels	Atherosclerosis Aneurysms
Lungs	Pulmonary congestion
Eye	Retinal hemorrhages Papilledema (edema around the optic disc)
Brain	Stroke (secondary to cerebral hemorrhage) Death (secondary to rupture of large vessel) Encephalopathy (cerebral edema)
Kidneys	Renal failure Proteinuria (secondary to renal vasculature damage)

Table 12.1: Causes of secondary hypertension

Systems	*Pathology*
Renal	Acute glomerulonephritis
	Renal artery stenosis
	Renal vasculitis
	Renin producing tumors
Endocrine	Acromegaly
	Hypothyroidism
	Hyperthyroidism
	Cushing's syndrome
	Conn's syndrome
	Pregnancy-induced
	Pheochromocytoma
	Exogenous hormones (contraceptives, glucocorticoids, and MAO inhibitors)
Cardiovascular	Increased cardiac output
	Coarcation of aorta
	Rigidity of aorta
	Increased intravascular volume
	Polyarteritis nodosa
Neurologic	Acute stress
	Psychogenic

Table 12.3: Management of hypertension
Lifestyle modifications
• Regular moderate exercise
• Reducing alcohol intake
• Restricting salt intake
• Good nutrition
• Giving up smoking
Drug Therapy
• Diuretics
• β-blockers
• ACE inhibitors
• Angiotension II receptor antagonists
• Calcium antagonists

Dental Considerations

The use of local anesthetic agents with vasoconstrictors in patients with cardiovascular disease remains controversial. The most commonly used vasoconstrictor is adrenaline. Vasoconstrictor restricts the spread and systemic side effects (e.g., dizziness, drowsiness, lightheadedness, blurred vision, slurred speech, muscle twitching, bradycardia, and hypotension) of lidocaine. Vasoconstrictor also prolongs the anesthetic effect of lidocaine.

Normal adrenaline release from the adrenal medulla can increase 20 to 40 fold during stress. Such stress may be induced by pain during dental treatment. Patients receiving local anesthetic without vasoconstrictor often have significantly impaired pain control compared with those receiving local anesthetic with adrenaline. For this reason, patients with cardiovascular disease may be at greater risk of experiencing massive endogenous adrenaline release secondary to poor local anesthesia than they are from the small amount of vasoconstrictor used in local anesthetics.

Most human studies examining hemodynamics (blood pressure, heart rate, heart rhythm, cardiac output, and myocardial oxygen requirement) after dental injection of 1.8 to 5.4 ml of 2% lidocaine with adrenaline (1:80,000) have found no significant changes in blood pressure or heart rate in healthy patients or in those with mild to moderate cardiovascular disease. Therefore, it is recommended that patients with mild to moderate cardiovascular disease receive the smallest amount of local anesthetic with vasoconstrictor needed to provide profound anesthesia, with aspiration performed to prevent intravascular injection. Exogenous vasoconstrictors may be contraindicated in patients with:

1. Hypersensitivity
2. Unstable angina
3. Recent myocardial infarction or coronary artery bypass surgery
4. Uncontrolled dysrhythmias
5. Severe hypertension
6. Severe congestive cardiac failure
7. Hyperthyroidism
8. Pregnancy

Intraligamentary injection of local anesthetics with vasoconstrictor is generally contraindicated in patients with severe cardiovascular disease, since the hemodynamics is similar to those observed after intravenous adrenaline injection.

ISCHEMIC HEART DISEASE

The most common cause of ischemic heart disease is atherosclerosis of the coronary arteries, and hence ischemic heart disease is often termed as coronary heart disease or coronary artery disease. The other causes of ischemic heart disease are coronary heart thrombosis and coronary artery vasospasm.

ATHEROSCLEROSIS

Atherosclerosis is a progressive disease characterized by lesions (atheromas or fibrofatty plaques) in the tunica intima of elastic arteries (e.g., aorta, carotid, and iliac arteries) and large to medium sized muscular arteries (e.g., coronary

and popliteal arteries). The impact of atherosclerosis on overall health is staggering. In some developing countries, atherosclerosis accounts for about 50% of deaths.

These atheromas consist of lipids primarily cholesterol and cholesterol esters, proliferating smooth muscle cells, and fat filled macrophages (monocytes) known as foam cells. The atheromas are covered with a fibrous capsule. As atheromas grow they spread along the artery wall forming swellings that protrude into the lumen and obstruct it. Critical stenosis is occlusion of the lumen of one or more coronary arteries to 75% or more by an atheroma.

Risk Factors

The four major risk factors are hyperlipidemia (increased low density lipoprotein (LDL) cholesterol levels), hypertension, cigarette smoking, and diabetes mellitus. Increased LDL cholesterol levels are due to consumption of egg yolk, animal fats, and dairy products (e.g., butter). The other risk factors for atherosclerosis are as follows:

1. Alcohol use
2. Genetic predisposition
3. Infection
4. Lower educational status
5. Males
6. Obesity
7. Older age group (60 years in men and 70 years in women)
8. Periodontitis
9. Poverty level
10. Sedentary life style
11. Socially isolated and divorced people

Infection

Sir William Osler in 1908 proposed that atherosclerosis itself was an infection. Infection is now recognized as one of the risk factor for atherosclerosis. There is evidence that infection with infectious agents such as *Sterptococcus sanguis*, *Chlamydia pneumonae*, *Helicobacter pylori*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Bacteroides forsythus*, and herpes virus is associated with atherosclerosis. People with severe periodontitis are highly predisposed to atherosclerosis as they have the greatest amounts of pathogenic bacteria, which may contribute to inflammatory response. The infectious agents can activate the inflammatory response, either *via* direct or indirect mechanisms.

1. **Direct:** The infectious agents may cause direct injury to the endothelium by recruitment and stimulation of proinflammatory (in favor of inflammation) cytokines (interleukin-1, prostaglandin E_2 and tumor necrosis factor-α) and tissue growth factors in the arterial wall and by enhancing the accumulation of LDL cholesterol through stimulation of LDL receptors.
2. **Indirect:** The infectious agents cause indirect injury to the endothelium by accelerating the inflammatory response caused by another agent e.g., hypertension. The indirect injury can either be due to release of endotoxin into the circulation by the infectious agents, which may indirectly damage the vascular endothelium or by systemic cytokine, which could predispose the arterial environment to procoagulant (in favor of coagulation) state, resulting in thrombus formation on a preexistent unstable plaque.

Pathogenesis

Considerable evidence has identified atherosclerosis as an inflammatory disease. This hypothesis, known as the Ross "Response to Injury Hypothesis" explains how inflammation is related to atherosclerosis. Ross hypothesis suggests that injury to the endothelium causes the initial lesion, leading to a chronic arterial

inflammatory process. The various risk factors that cause injury to the endothelium have been mentioned earlier. During this inflammatory process, monocytes and platelets adhere to the endothelium and migrate between endothelial cells into the tunica intima. This is followed by release of growth factors, including platelet derived growth factor (PDGF), which leads to smooth muscle migration from tunica media into the tunica intima. The macrophages and smooth muscle cells engulf LDL (cholesterol and cholesterol esters), to become foam cells. The LDL are derived from the blood vessel lumen, particularly in the presence of hyperlipidemia and from degenerating foam cells. The smooth muscle cells produce large amounts of extracellular matrix, including collagen and proteoglycans forming atheroma or fibrofatty plaque.

With progression the atheroma becomes prominent on the intimal aspect, producing a fibrous cap. The occlusion of small arteries by an atheroma leads to ischemia (decreased blood supply) and infarction of the tissues. The focal rupture of the fibrous cap may result in thrombus formation.

Coronary Heart Thrombosis

Focal rupture of an atheroma involving the coronary artery exposes the underlying thrombogenic lipids, and subendothelial collagen which initiate platelet aggregation, thrombin generation, and ultimately thrombus formation. The platelet aggregates release vasospastic mediators such as thromboxane A_2, causing vasospasm.

Coronary Artery Vasospasm

Coronary artery vasospasm is probably due to release of vasospastic mediators such as thromboxane A_2, by platelet aggregates after the rupture of an atheroma and reduced synthesis of vasodilators (nitric oxide and prostacyclin) by the endothelial cells.

Ischemic Heart Diseases

Depending upon the severity of coronary artery narrowing and myocardial response, ischemic heart diseases are classified as:

1. Angina pectoris
2. Myocardial infarction

If the coronary artery is completely occluded by an atheroma or thrombus, acute myocardial infarction occurs. In contrast, if the coronary artery is partially occluded by an atheroma or thrombus, the patient may develop unstable angina (Fig.12.6).

Angina Pectoris

Typical or stable angina pectoris

Typical or stable angina pectoris refers to episodic chest pain associated with exertion or some other form of stress. The pain is classically described as a crushing or squeezing retrosternal sensation, which may radiate down to the left arm, mandible, shoulder, and neck. Stable angina pectoris is usually associated with a fixed occlusion (75% or more) of one or more coronary arteries by fixed atheroma. With this degree of occlusion, the myocardial oxygen demand may be adequate under normal conditions but is not sufficient to meet the increased requirements imposed by exercise or other conditions that stress the heart.

The pain is usually relieved by rest or by administration of sublingual glyceryl trinitrate. The main action of sublingual glyceryl trinitrate is to cause dilatation of the capacitance vessels as a result of which there is decreased venous return and decreased cardiac output

In large doses sublingual glyceryl trinitrate may increase the blood supply to the myocardium by causing vasodilatation of the coronary arteries.

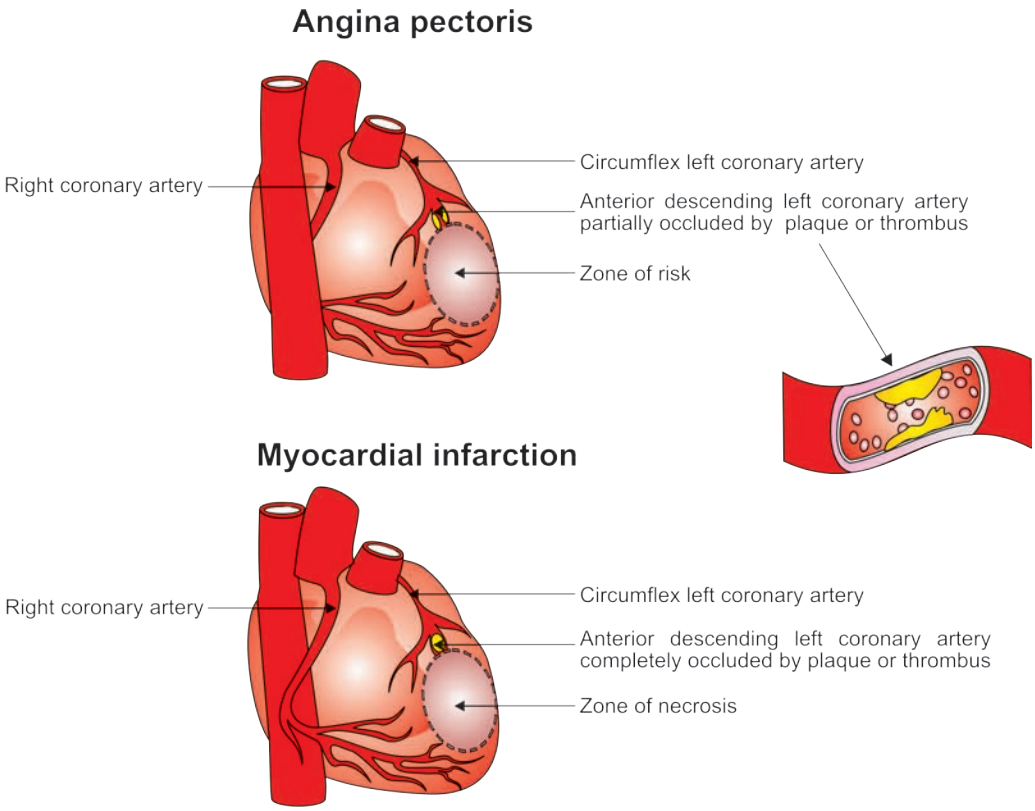

Fig. 12.6: Angina pectoris and myocardial infarction

Prinzmetal angina

Prinzmetal Angina or variant angina refers to angina that occurs at rest or in some cases, awakens the patient from sleep. Angiographic studies have shown that prinzmetal angina is associated with coronary artery vasospasm. The cause of vasospasm is not clear but exposure to cold weather and emotional stress may precipitate the secretion of endogenous adrenaline and noradrenaline, which increases the vascular tone of coronary blood vessels causing vasoconstriction. Although the vasospasm usually occurs near an atherosclerotic plaque, it may affect a normal blood vessel.

Unstable angina pectoris

Unstable angina pectoris or crescendo angina is characterized by the increased frequency of anginal pain, which is precipitated by less exertion. The attack is more intense and often lasts longer than stable angina pectoris. Unstable angina pectoris is usually associated with incomplete luminal occlusion by the thrombus. Unstable angina pectoris is sometimes referred to as preinfarction angina as it may develop into acute myocardial infarction.

Acute Myocardial Infarction

An infarct is an area of necrotic tissue that has died because of lack of oxygenated blood. When

a branch of coronary artery is completely occluded by a thrombus, overlying the ruptured atheroma, acute myocardial infarction occurs because of lack of oxygenated blood to the myocardium. Acute myocardial infarction is also known as "heart attack". The risk of acute myocardial infarction increases progressively throughout life. Between ages of 45 and 54, men are 4 to 5 times as likely to develop acute myocardial infarction as women. However, after 80 years the risk factor is same in both sexes.

Pathogenesis

Angiographic studies indicate that most acute myocardial infarctions are caused by coronary artery thrombosis. Infarction of the myocardium begins within 20 to 30 minutes of the coronary artery occlusion. The subendocardial region of the myocardium is the most poorly perfused region because it is the last area to receive blood supply from branches of the coronary arteries. The high intramural pressure further compromises the blood flow to the subendocardium Because of this the subendocardium is vulnerable to ischemic injury and the infarction typically begins in the subendocardial region.

Although infarction proceeds from the subendocardium to epicardium, a very narrow zone of myocardium immediately beneath the endocardium is spared from infarction because it can be oxygenated by diffusion from the ventricle. The infarct usually reaches its full size within 3 to 6 hours. During this period, lysis of the thrombus by the administration of thrombolytic agents (alteplase or streptokinase) may limit the size of the infarct.

The location of myocardial infarction is determined by the site of the vascular occlusion and by the anatomy of the coronary circulation. Occlusion of the right coronary artery causes infarction of the posterior wall of the left ventricle, and posterior one third of interventricular septum. Occlusion of the anterior descending left coronary artery causes infarction in the anterior and apical areas of the left ventricle, and anterior two thirds of the interventricular septum. Occlusion of circumflex left coronary artery causes infarction of lateral wall of the left ventricle. If the thrombus occludes proximal segments (situated near to the point of origin) of the coronary arteries, the size of the infarct is large. If the thrombus occludes distal segments (situated far from the point of origin) of the coronary arteries, the size of the infarct is small.

Types of Acute Myocardial Infarction

When the myocardial infarct involves most of the thickness of the ventricular wall, they are refered to as transmural infarcts, while those restricted to inner subendocardial region (the inner one third of the myocardium) are designated as subendocardial infarcts.

Clinical Features

Acute myocardial infarction is usually accompanied by severe, crushing retrosternal pain, which may radiate to the neck, jaw, epigastrium, shoulder, or left arm. The pain associated with acute myocardial infarction typically lasts for several hours to days and is not relieved by sublingual glyceryl trinitrate. The other clinical features are weak and rapid pulse, dyspnoea (pulmonary congestion and edema due to impaired contraction of ischemic myocardium).

Electrocardiographic (ECG) Abnormalities

When the blood supply to the myocardium is interrupted, there are irreversible changes (ischemia and necrosis) in the myocardium that

produce various ECG abnormalities. The ECG abnormalities associated with acute myocardial infarction are deep Q wave, loss of R wave, elevation and depression of ST segment, elevation and depression of T wave. Thus, the ECG is very useful in diagnosing and locating areas of infarction.

Laboratory Evaluation

Laboratory evaluation is an integral part in the diagnosis of acute myocardial infarction. A number of enzymes and proteins are released into the circulation by the dying myocardial cells. Measurement of the level of some of these enzymes or proteins in the serum is helpful in the diagnosis of acute myocardial infarction. Increased serum creatinine kinase within 72 hours of acute myocardial infarction is suggestive of acute myocardial infarction. Increased levels of troponins within 7 days after attack of acute myocardial infarction are suggestive of acute myocardial infarction.

Complications

1. Dysrhythmias or arrhythmias
2. Heart block (impaired conduction of impulses) due infarction of the myocardium
3. Congestive cardiac failure due to impaired contraction of the myocardium
4. Rupture of ventricular wall usually within 2 weeks of original episode
5. Mural thrombi, which develop on the endocardial surface overlying the infarct, are potential sources for pulmonary embolism, and cerebral embolism.
6. Pericarditis
7. Angina pectoris
8. Recurrence

Management of Acute Myocardial Infarction (Figs.12.7, Table 12.4 and 12.5)

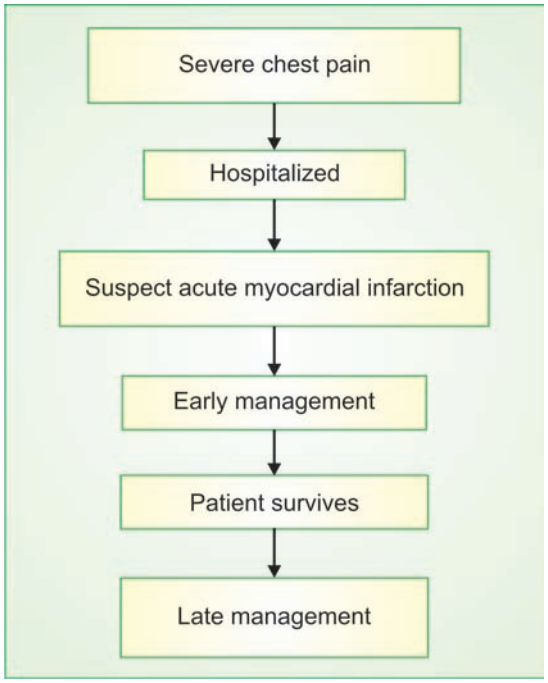

Fig. 12.7: Management of acute myocardial infarction

Dental Considerations

The medications most commonly used to treat patients with stable angina include glyceryl trinitrate, β_1 receptor blocking agents, and calcium channel blockers (e.g., amlodipine). It is clear from the literature that psychological or physiological stress may exacerbate ischemic symptoms. Therefore, use of a stress reduction protocol and profound (heavy) anesthesia is an integral part of dental treatment for such patients. Dental treatment planning may be altered in these patients. The duration of the treatment should be short, small amount of local anesthetic with vasoconstrictor should be used, and if indicated preoperative or intraoperative conscious sedation should be performed.

Table 12.4: Early management of acute myocardial infarction
Provide facilities for defibrillation
Immediate measures
• 100% oxygen • i.v. analgesics (e.g., morphine sulphate) and antiemetics (e.g., meclozine); analgesics and antiemetics should not be administered intramuscularly because of delay in clinical effect due to poor skeletal muscle perfusion • ECG monitoring
Reperfusion of the myocardium
• Thrombolytic agents such as alteplase or streptokinase; thrombolytic agents cause coronary artery thrombolysis and help restore coronary patency • Primary percutaneous coronary intervention (PCI) of affected coronary artery; It is a safe and effective alternative to thrombolytic therapy
Detection and management of complications
• Dysrhythmias • Left ventricular failure • Cardiac failure

Table 12.5: Late management of acute myocardial infarction
Life style modification
• Stop smoking • Regular exercise • Diet (weight control, lowering of LDL levels)
Secondary prevention drug therapy
• Antiplatelet therapy e.g., aspirin or warfarin • β_1 receptor blocking agents e.g., atenolol • ACE inhibitors e.g., captopril • Atorvastatin (reduces the LDL level) • Additional therapy for diabetes and hypertension
Rehabilitation

Supplemental oxygen delivered *via* a nasal canal may help prevent intraoperative anginal attacks. The drugs of choice for treating an acute anginal attack are 100% oxygen and sublingual glyceryl trinitrate (300-600 mcg repeated three times within 15 minutes if necessary). The patient should be instructed to bring his or her own glyceryl trinitrate tablets for each appointment, and the dentist should have glyceryl trinitrate tablets in the emergency medical kit.

Patients with unstable angina generally are not candidates for elective dental therapy, and consultation with the patients physician usually is indicated. If emergency dental care is needed, preoperative anxiolytic agents may be indicated for stress reduction and to minimize endogenous adrenaline release. The dentist should closely monitor the patients hemodynamic status and oxygen saturation before and during treatment.

It is commonly recommend that patients not receive routine dental care for at least 6 months after experiencing a myocardial infarction. This recommendation is based on the fact that the peak mortality rate (death rate) following myocardial infarction occurs during the first year, primarily resulting from the increased electrical instability of the myocardium after the infarction. After the six-month post-myocardial infarction period, most patients may be treated with techniques similar to those used for the patient with stable angina, including relatively short appointments and a stress-reduction protocol where indicated.

Anticoagulant Therapy

Patients with history of valvular heart disease, myocardial infarction, and cerebrovascular accident frequently receive anticoagulant therapy consisting of aspirin or warfarin. Therefore, the dentist should consult with the patients physician before the dental treatment (as it may induce bleeding) to determine whether modification of anticoagulant therapy is indicated.

Aspirin, an inhibitor of platelet aggregation, often is used to prevent thrombosis formation.

Because of its irreversible binding to platelets, the effect of aspirin lasts at least 4 to 7 days. Aspirin is generally used in small doses of 75 mg (150-300 mg loading dose followed by 150 mg daily for the 1st month and then 75 mg daily thereafter) and usually will not alter bleeding time significantly at this dose. However, higher doses may increase bleeding time and predispose the patient to develop postoperative bleeding. For these patients, aspirin therapy should be modified or discontinued for several days before the dental procedure.

VALVULAR HEART DISEASES

The heart valves prevent backflow of the blood in the heart during the cardiac cycle. Distinctive heart sounds are produced during the cardiac cycle when the valves close. Damaged valves generate abnormal heart sounds called murmurs.

The most common causes of valve defects are rheumatic fever, infective endocarditis, and congenital abnormalities. The mitral and aortic valves are subjected to high pressure stresses than the tricuspid valves and the pulmonary valve. Therefore, the mitral and aortic valves are commonly affected, the tricuspid valve sometimes and the pulmonary valve rarely.

1. **Stenosis:** Stenosis is defined as pathological narrowing of the cardiac valve orifice e.g., narrowing of the aortic valve orifice. Stenosis occurs when there is deposition of vegetations (a clot composed blood platelets, fibrin, and bacteria adherent to the heart valve) on the cusps along their line of closure, which results in adherence of the valve edges. These vegetations tend to become organized, resulting in the formation of fibrous scar tissue. The fibrous scar tissue shrinks as it ages and distorts the shape of the cusps and causes stenosis, incompetence, and regurgitation.
2. **Incompetence:** Incompetence is defined as defective closure of the cardiac valve e.g., defective closure of the aortic valve permitting backward flow of blood (regurgitation) into the left ventricle during ventricular diastole. Incompetence occurs when the edges of the valves are destroyed by fibrous scar tissue resulting in defective closure and regurgitation.

Rheumatic Fever

Rheumatic fever is an autoimmune disease in which the heart valves are likely to be damaged or destroyed. The fact that symptoms typically do not develop until 2 to 3 weeks after infection and that the streptococci are absent from the lesions supports the concept that rheumatic fever results from an immune response against streptococci.

Etiology

Rheumatic fever occurs 2 to 4 weeks after a preliminary infection (pharyngitis, scarlet fever, or middle ear infection) caused by *Sterptococcus pyogenes* (group A β-hemolytic streptococci). *Streptococcus pyogenes* produces numerous virulence factors. One of the most important virulence factor is the antiphagocytic cell wall M protein. *Sterptococcus pyogenes* also elaborates 20 extracellular products, which include enzymes such as streptolysins, hyaluronidase, streptokinase, deoxyribonucleases (DNases), nicotinamide adenine dinucleotidase (NADase), and pyrogenic toxin (erythrosine). Neither streptolysins (streptolysin O and streptolysin S) has a proven role in the pathogenesis of human disease. Streptokinase promotes fibrinolytic activity by converting plasminogen to plasmin, and hyaluronidase may enhance the spread of organism through the connective tissue. The

pathogenic significance of DNases and NADase is unknown. The pyrogenic action of erythrosine is due to direct action on the hypothalamus.

Pathogenesis

The pathogenesis of rheumatic fever is not fully understood. It has been proposed that preliminary infection caused specifically by *Sterptococcus pyogenes* evokes an autoimmune response. This preliminary infection is followed by production of antibodies against antiphagocytic cell wall M protein of *Sterptococcus pyogenes*, which then cross react with normal proteins present in the heart (cardiac myosin and sarcolemmal membrane protein), joints, and other tissues. These reactions take place as long as the antibodies persist in the blood (i.e., for 1 year or more). Rheumatic fever causes damage to many parts of the body especially the heart, joints, and skin.

Heart

Rheumatic pancarditis is characterized by inflammatory changes in all three layers of heart i.e., pancarditis (Table 12.6).

1. **Pericardium:** Inflammation of the pericardium leads to the accumulation of serous exudates in the pericardial space. Healing is accompanied by obliteration of pericardial space due to fusion of outer parietal and inner visceral pericardium and fibrous thickening of the pericardium. Because of fibrous thickening of pericardium the heart may not be able to expand fully during systole, leading to reduced cardiac output, generalized venous congestion and edema.
2. **Myocardium:** The hallmark of rheumatic fever is the presence of multiple foci of inflammation within the myocardium, called Aschoff bodies. The Aschoff's bodies consist of central area of necrotic collagen surrounded by a zone of inflammatory cells polymorphs, macrophages, and Aschoff's giant cells. The Aschoff's giant cells or Anitschkow cells are large macrophages with multiple vesicular nuclei (upto 4) and abundant eosinophilic cytoplasm. The Aschoff bodies ultimately undergo fibrosis.
3. **Endocardium:** Valvulitis (inflammation of the heart valves) is common in rheumatic fever when the endocardium is involved and is the most important lesion of rheumatic fever. The degree of heart valve damage is directly correlated with the antibody titer and the persistence of these antibodies. Valvulitis is most pronounced in mitral and aortic valves than tricuspid and pulmonary valves. Valvulitis is characterized by deposition of small vegetations on the cusps along their line of closure. These vegetations tend to become organized, resulting in the formation of fibrous scar tissue. The fibrous scar tissue shrinks as it ages and distorts the shape of the cusps and causes stenosis, incompetence, and regurgitation. The mitral valve orifice looks stenotic, appearing as pinhole, sometimes designated as "fish-mouth deformity."

Table 12.6: Features of pancarditis

- Dyspnoea (due to pericarditis or congestive cardiac failure)
- Chest pain (due to pericarditis)
- Pericardial rub (due to pericarditis)
- Carey Coombs murmur (a soft mid diastolic murmur due to valvulitis)
- Heart block (due to fibrosis of the myocardium)
- Congestive cardiac failure due to impaired contraction of myocardium

Joints

The joints are red, swollen, and tender. Migrating polyarthritis typically involves the ankles, knees, elbows, and wrists sequentially (consecutively). The pain characteristically responds to aspirin.

Skin

Skin changes take the form of erythema marginatum. Clinically erythema marginatum appears as a maculopapular rash mainly on the trunk and proximal extremities but not on the face. Microscopically, erythema marginatum appears as large Aschoff's bodies.

Sydenham's Chorea (St Vitus dance)

Sydenham's chorea named after English physician, Thomas Sydenham, is commonly associated with streptococcal throat infection, rheumatic fever and infective endocarditis and is characterized by rapid uncoordinated, involuntary muscle movements. In mild cases, recovery takes place within 4 weeks and in some cases recovery may be followed by recurrences.

Clinical Features

Rheumatic fever is a disease of childhood and affects those between 5 and 15 years of age. It typically occurs 2 to 4 weeks after the preliminary infection. It is interesting to note that rheumatic fever rarely follows infections by *Streptococci pyogenes* at other sites, such as the skin. Rheumatic fever is characterized by fever, pancarditis, migrating polyarthritis, erythema marginatum, and Sydenham's chorea.

While most of the other lesions of rheumatic fever undergo resolution, those of the valves do not and tend to progress to a state of chronic inflammation where the valves become fibrosed and distorted. Damaged valves predispose the patients to infective endocarditis.

Diagnosis

The diagnosis according to the revised Jones criteria (Table 12.7) is based upon two or more major manifestations, or one major and two or more minor manifestations; evidence of preceding streptococcal infection is also required. When diagnosing rheumatic fever, only 25% of patients with have positive culture for group A β-hemolytic streptococci because there is a latent period between infection and presentation. Blood or chocolate agar is preferred because the hemolytic properties of streptolysins can be assessed. Serological evidence of recent streptococcal infection may be helpful (Table 12.8).

Table 12.7: Jones criteria for diagnosis of rheumatic fever

Major manifestations
• Pancarditis • Migratory polyarthritis • Erythema marginatum • Sydenham's chorea (St Vitus dance)
Minor manifestations
• Fever • Arthralgia • History of previous rheumatic fever • Leucocytosis • Raised ESR • First or second degree heart block
Evidence of recent streptococcal infection
• Increased titre of antistreptolysin O antibody titre or antibodies against antiphagocytic cell wall M protein; positive throat swab culture
N.B. Evidence of recent streptococcal infection is particularly important if there is only one major manifestation

Table 12.8: Investigations in acute rheumatic fever

Evidence of systemic illness (Nonspecific)
• Leucocytosis • Raised ESR • Raised C-reactive protein
Evidence of recent streptococcal infection (Specific)
Throat swab culture: Group A β-hemolytic streptococci Increased titres of antistreptolysin O antibodies: > 200 units (adults) or > 300 units (children)
Evidence of pancarditis
Chest radiograph: Cardiomegaly; pulmonary congestion ECG: First and second degree heart block; features of pericarditis; T wave inversion; reduction in QRS voltages Echocardiography: Cardiac dilation and valve abnormalities

Management

Management of rheumatic fever includes bed rest (due to which the joint pain is minimized, and cardiac output is reduced in patients with pancarditis), and administration of antibiotics e.g., benzathine penicillin G or sulphadiazine or erythromycin (if allergic to benzathine penicillin G or sulphadiazine), analgesics, and corticosteroids (indicated in cases with pancarditis and severe arthritis).

Infective Endocarditis

Infective endocarditis is a condition in which the heart valves are invaded by microorganisms, usually bacteria and hence the name "bacterial endocarditis." However, apart from bacteria, other microorganisms like fungi and viruses are capable of causing this condition and hence the name "infective endocarditis."

The hallmark of infective endocarditis is the presence of large friable (light) vegetations on the heart valves. The vegetations consisting of platelets and fibrin surround the microorganisms and seem to protect them from normal body defenses and antibiotics. The vegetations may be single or multiple and may involve more than one valve. The appearance of the vegetations is influenced by the type of microorganism responsible for the infection, the degree of host immune response to the infection, and previous antibiotic therapy for e.g., *Candida albicans* tends to cause larger vegetations than bacterial infection. The aortic and mitral valves are the most commonly affected, although the tricuspid valve may also be involved particularly in intravenous drug abusers.

Etiology

Virtually any type of microorganism is capable of causing infective endocarditis, although most cases are caused by bacteria. Bloodborne bacteria (bacteremia) are the requirements for infective endocarditis, acute and subacute. Bacteremia may result due to infection elsewhere in the body e.g., periodontitis, dental treatment procedures, mastication, brushing of teeth, surgical procedures, and urinary catheterization. Infection occurs when microorganisms are implanted on the endocardial surface during episodes of bacteremia.

Bacteria causing infective endocarditis have been subdivided into two groups: high virulence and moderate to low virulence. Coagulase positive *Staphylococcus aureus* is highly virulent and is a common cause of acute endocarditis. The viridans groups of streptococci (*Streptococcus mitis, Streptococcus sanguis, and* α hemolytic streptococci) are low virulent commensals in the oral cavity and are common causes of subacute endocarditis.

Risk Factors

Factors that increase the risk of infective endocarditis can be subdivided into four categories.

1. **Previous cardiac abnormalities:** Any cardiac abnormality that increases the hemodynamic trauma to the endocardial surface such as high pressure shunts within the heart (e.g., ventricular septal defect) or chronic valvular diseases (e.g., rheumatic fever) increase the risk of infective endocarditis.
2. **Prosthetic heart valves:** Prosthetic valves are of two types: mechanical and bioprosthetic valves (derived from bovine or porcine tissues). Prosthetic heart valves undergo some degree of stiffening after implantation causing stenosis, which may predispose to infective endocarditis. Infective endocarditis in prosthetic heart valve patients is caused by coagulase negative *Staphylococcus epidermis*.
3. **Intravenous drug abusers:** Intravenous drug abusers are at high risk for development of infective endocarditis because they inject

contaminated material directly into the blood. Infective endocarditis in intravenous drug abusers occurs on previously normal valves, often involving the tricuspid valve. The causative organism of infective endocarditis in intravenous drug abusers is *Staphylococcus aureus*, which is commonly found in the skin.

4. **Immunosupression:** Immunosupression enables low virulence microorganisms such as α-hemolytic streptococci, fungi, and viruses to become established and cause infection.

Classification

Infective endocarditis has been traditionally subdivided into acute and subacute endocarditis.

1. **Acute Endocarditis:** Acute endocarditis is typically caused by highly virulent organisms (e.g., *Staphylococcus aureus*) but sometimes other microorganisms (e.g., *Streptococcus pneumoniae* and *Neisseria gonorrhoeae*) are responsible. During the course of bacteremia, the staphylococci may invade the previously normal heart valves and produce endocarditis, which is characterized by the deposition of large friable vegetations on the valve surface. The vegetations in acute endocarditis begin as small excrescences (protrusions) but as the microorganisms proliferate, the vegetations enlarge and eventually become large and friable that may obstruct the valve orifice. The vegetations may cause rapid destruction of the valves, chordae tendineae, and papillary muscle resulting in cardiac failure. The infection may eventually extend into the adjacent myocardium to produce abscess often known as ring abscess. The vegetations are large, and friable, and tend to break off and embolize to spleen, kidneys, heart, and brain resulting in infarction and metastatic infection (abscesses) because the embolic fragments contain large number of virulent organisms. When the vegetations break off and embolize the microorganisms are exposed to the bactericidal action of the blood resulting in the formation of antigen-antibody complexes.
2. **Subacute Endocarditis:** Subacute endocarditis is typically caused by moderate to low virulent organisms most frequently *Streptococcus viridans,* but sometimes other microorganisms e.g., *Candida albicans* are responsible. During the course of bacteremia, the streptococci may invade the previously injured or abnormal heart valves to produce subacute endocarditis, which is characterized by the deposition of small friable vegetations on the valve surface, and may embolize with less frequent complications. The vegetations of subacute endocarditis are distinguished from those of acute endocarditis by the presence of granulation tissue, which attaches the vegetations to the valves.

Clinical Features

1. **Acute endocarditis:** Acute endocarditis typically presents as rapidly developing fever with rigors, malaise, weight loss, petechiae (due to microemboli or antigen-antibody complexes), and changing cardiac murmurs. The larger vegetations often cause embolic complications and there frequently is splenomegaly. Cardiac failure and renal failure develop rapidly. Even with treatment, death occurs in days to weeks in 50 to 60% of the patients.
2. **Subacute endocarditis:** Subacute endocarditis should be suspected when the patient is known to have any previous cardiac abnormalities such as ventricular septal defect, mitral valve prolapse, and rheumatic fever. It typically has an insidious onset with low grade fever, malaise, weight loss, and flu-like syndrome. Other features include

subconjuctival hemorrhages, petechiae on the skin and mucous membranes, splincter hemorrhages under the finger or toe nails, Osler's nodules at the finger tips due to vasculitis, digital clubbing, splenomegaly, and hematouria.

Clinical Complications

1. Direct injury to the heart valves
2. Formation of ring abscess
3. The vegetations are large, and friable, and tend to break off and embolize to spleen, kidneys, heart, and brain resulting in metastatic infection and infarction.

Diagnosis

Diagnosis is confirmed by blood culture. However, if the clinical picture suggests endocarditis, treatment should begin without waiting for pathological confirmation. Echocardiography is helpful in detecting vegetations and ring abscess. Urine examination reveals microscopic hematouria. ECG may show abnormalities due to ring abscess formation.

Treatment

Treatment consists of multidisciplinary approach between physician, surgeon, and microbiologist. The treatment regimen consists of removing the source of infection (e.g., periodontitis) and antimicrobial treatment consisting of intravenous administration of benzylpenicillin or vancomycin in patients who are allergic to penicillin.

Vancomycin plus gentamycin is recommended for staphylococcal endocarditis. Cardiac surgery is advisable when there are large vegetations (increased risk of systemic embolization), heart failure due to valve damage, failure of antibiotic therapy, and the presence of ring abscesses.

Dental Considerations

The most important goal of dental treatment in patients with valvular heart disease is to prevent infective endocarditis. The dental treatment procedures known to induce gingival or mucosal bleeding may often cause transient bacteremia that rarely lasts longer than 15 minutes. However, within these 15 minutes the bacteria may lodge (stick) themselves on previously injured or abnormal heart valves, which may result in infective endocarditis. Although bacteremia is common following many invasive procedures, only certain bacteria usually cause infective endocarditis. It is not always possible to predict which patients will develop this infection or which particular procedure will be responsible.

The percentage of patients with infective endocarditis who received recent dental treatment procedures varies from 3 to 40%. Most cases of infective endocarditis involving oral microorganisms are not likely to be caused by dental treatment procedures, but by dental diseases, mastication, and brushing of teeth. Certain cardiac conditions are associated with infective endocarditis more often than others. Antibiotic prophylaxis is recommended in individuals who have a high risk of developing infective endocarditis. The patients with cardiovascular diseases, who are associated with infective endocarditis, are grouped into:

1. **Negligible-risk category:** The low-risk category includes patients with implanted cardiac pacemakers (intravascular and epicardial), automatic defibrillators, and a previous history of coronary artery bypass surgery.
2. **Moderate-risk category:** The moderate-risk category includes patients with patent ductus arteriosus, atrial septal defect, ventricular septal defect, coarctation of the aorta, bicuspid aortic valve, acquired valvular dysfunction (e.g., due to rheumatic heart fever or collagen vascular disease), and hypertrophic cardiomyopathy.

3. **High-risk category:** The high-risk category includes patients with prosthetic heart valves (mechanical and bioprosthetic), a previous history of infective endocarditis, complex cyanotic congenital heart disease (e.g., Fallot's tetralogy), and surgically constructed systemic pulmonary shunts.

The antibiotic prophylaxis for infective endocarditis should consider:

1. The degree to which the patients underlying condition creates a risk of endocarditis
2. The apparent risk of bacteremia with the procedure
3. The potential side effects of the prophylactic antibiotic
4. The cost-benefit aspects of the recommended prophylactic antibiotic regimen.

Failure to consider all of these factors may lead to overuse, excessive cost and risk of adverse drug reactions. The American Heart Association (AHA) recommends antibiotic prophylaxis (Table 12.9) prior to dental treatment procedures (e.g., dental extractions, periodontal surgery, dental implant surgery, intraligamentary local anesthetic injection, initial placement of orthodontic bands, and periapical surgery) known to induce gingival or mucosal bleeding. In order to reduce microbial resistance and potential side affects, it is important that the antibiotic prophylaxis should be initiated one hour before the procedure and should not be continued for more than 6 to 8 hours.

Alternatively, numerous dental treatment procedures may be accomplished at the same appointment, and if possible as a local accessory to systemic antibiotic prophylaxis, a chlorhexidine gluconate 0.20% solution mouth rinse can be used before dental treatment procedures. In case of delayed healing, it may be necessary to provide additional doses of antibiotics for treatment. It is advisable to administer antimicrobial prophylaxis before a dental treatment procedure that involves infected tissues. Prophylaxis should be directed at the most likely pathogen causing the infection.

Table 12.9: Antibiotic prophylaxis against subacute endocarditis

Situation	*agent*[†]	*regimen*[‡]
Standard prophylaxis	Amoxycillin	Adults, 2.0 grams; children, 50 mg/kg orally 1 hour before procedure
Unable to take oral medications	Ampicillin	Adults, 2.0 g IM[††] or IV[§;] ; children, 50 mg/kg IM[††] or IV[§] within 30 minutes before procedure
Allergic to penicillin	Clindamycin	Adults, 600 mg; children, 20 mg/kg orally 1 hour before procedure
	Cefalexin or cefadroxil	Adults, 2.0 g; children, 50 mg/kg orally 1 hour before procedure
	Azithromycin or clarithromycin	Adults, 500 mg; children, 15 mg/kg orally 1 hour before procedure
Allergic to penicillin and unable to take oral medications	Clindamycin	Adults, 600 mg; children, 20 mg/kg IV[§] 1hour before procedure
	Cefazolin	Adults, 1.0 g; children, 25 mg/kg IM[††] or IV[§] within 30 minutes before procedure

[†] Cephalosporins should not be used in patients with immediate-type hypersensitivity reaction (urticaria, angioedeman or anaphylaxis) to penicillins

[‡] Total children's dose should not exceed adult dose

[††] IM: intramuscular

[§] IV: intravenous

CEREBROVASCULAR ACCIDENT AND DYSRHYTHMIAS

Stroke

A stroke results from sudden interruption of blood flow to the brain, which deprives it of oxygen. When the blood vessel that delivers oxygen and nutrients to the brain is obstructed by atherosclerosis or embolus, the condition is called ischemic stroke or cerebral ischemia (Fig.12.8). Hemorrhagic stroke occurs when a blood vessel supplying the brain ruptures and causes bleeding into the brain. In any form of stroke, the nerve cells of the brain are deprived of oxygen and die within minutes of onset of the stroke. Therefore, a stroke can cause impairment of body functions such as speech, memory, and movement that are controlled by the affected portion of the brain. The risk factors include smoking, hypertension and diabetes mellitus.

Oral Manifestations

Dysphasia (lack of coordination in speech) may be present in the patient with stroke and can cause changes in diet, mastication, nutrition, and body weight. Inability to completely clear food in the mouth may result in halitosis, caries, gingivitis and periodontitis.

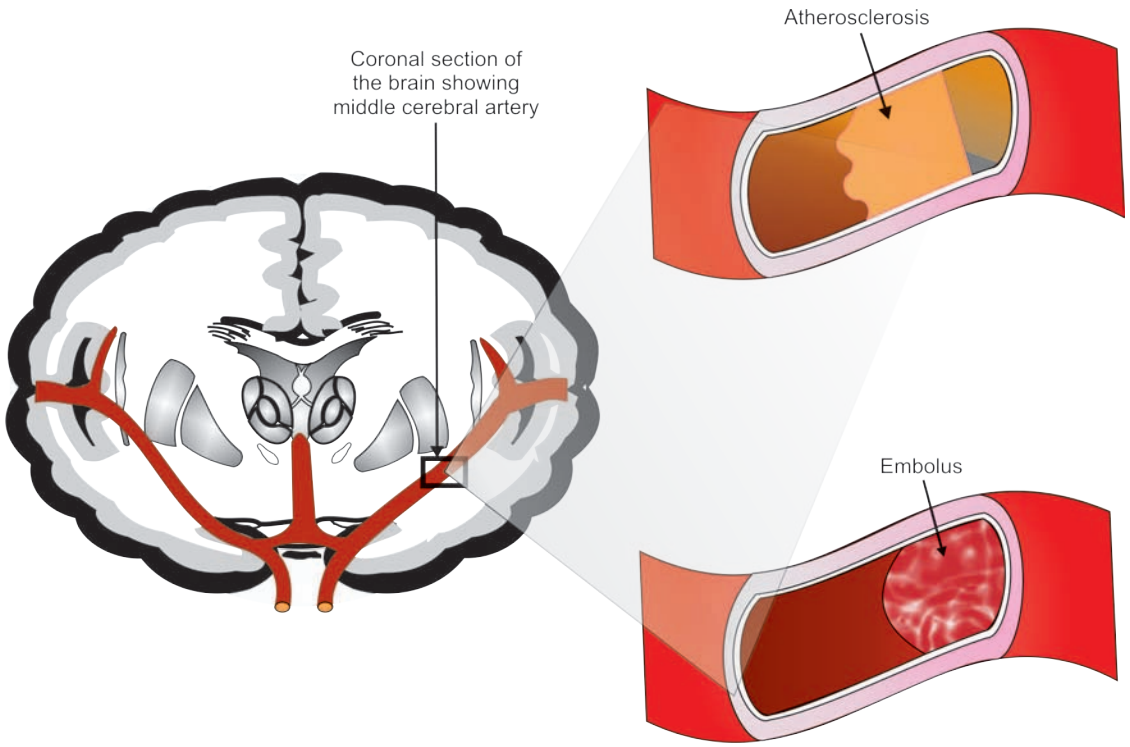

Fig. 12.8: Stroke

Dental Considerations

1. Patients with stroke are frequently treated with oral anticoagulants therefore; the dentist should consult the concerned physician before treatment to determine whether anticoagulant therapy should be modified
2. To prevent a subsequent stroke, clinicians must treat active infections aggressively, since even minor infection may alter blood coagulation and trigger thrombus formation ensuing in cerebral infarction
3. Weakness of the facial area or paralysis of extremities may make oral hygiene procedures extremely difficult; therefore, the dentist in consultation with an occupational therapist may modify oral hygiene instruments for ease of use
4. The patients head position should be adjusted, while constant evacuation will prevent aspiration of foreign matter
5. The gag reflex may be diminished after a stroke, which may require particular attention during dental therapy
6. The dentist should counsel the patient about the importance of oral hygiene and may initiate a long-term regimen of chlorhexidine gluconate 0.20% solution to help in plaque control

DYSRHYTHMIAS

Dental Considerations

Many of the antidysrhythmic drugs have side effects such as gingival overgrowth or xerostomia. The use of local anesthetics with vasoconstrictors may be contraindicated in patients with uncontrolled dysrhythmias; dental treatment may best be accomplished in a hospital setting with careful cardiac monitoring. Some dysrhythmias are treated with implanted cardiac pacemakers or automatic defibrillators in addition to drug therapy.

Pacemakers and automatic defibrillators present a low risk of infective endocarditis and do not require prophylactic antibiotic coverage before dental therapy. Older pacemakers were unipolar and were affected by equipment that generates an electromagnetic field, such as ultrasonic scalers and electrocautery units. Most pacemakers placed within the last 30 years are bipolar and generally are not affected by the small electromagnetic fields created by dental equipment.

Automatic defibrillators are often activated-without warning, which may cause sudden movement and endanger the patient in the dental chair. The dentist must be aware of this potential problem during treatment, and should stabilize the operating field through use of a bite-block with floss (for easy retrieval) and rubber dam.

SUMMARY

Dental Management of Patients with Cardiovascular Disease

The primary goal in the management of a patient with cardiovascular disease during dental treatment is to minimize any alterations in hemodynamics during treatment (i.e., by maintaining the patients blood pressure, heart rate, heart rhythm, cardiac output and myocardial oxygen requirement). Psychological and physiological stress during dental treatment has the potential to alter the hemodynamics significantly. Therefore, a stress-reduction protocol is frequently suggested for patients with significant cardiovascular compromise, which includes the following:

1. Shorter appointments, preferably in the morning when the patient is well-rested and has a additional physical energy
2. Use of profound local anesthesia to minimize discomfort
3. Preoperative or intraoperative (during the procedure) conscious sedation or both
4. Postoperative analgesia

II. ASTHMA AND DENTAL CARE

Respiratory problems such as asthma affect many aspects of dental treatment. Extracting a proper history from the patient with asthma will help prevent serious problems and alert the dentist to orofacial conditions e.g., oro-pharyngeal candidosis, which may result from the use of appropriate medication (corticosteroid inhalers). Patients with severe persistent asthma or status asthmaticus are best treated in the hospital setting.

NORMAL ANATOMY OF THE RESPIRATORY TRACT

Trachea

The trachea (windpipe) is a continuation of the larynx and extends downwards to about the level of the 5th thoracic vertebra where it divides at the carnia into right and left bronchi, one bronchus going to each lung. Structures associated with the trachea are:

1. **Superiorly:** The larynx
2. **Inferiorly:** The right and left bronchi
3. **Anteriorly:** The isthmus of the thyroid gland
4. **Posteriorly:** The esophagus, which separates the trachea from the vertebral column.
5. **Laterally:** The apex of the lungs and the lobes of the thyroid gland

Structure

The trachea is composed of 16 to 20 incomplete C-shaped rings of hyaline cartilages lying one above the other. The cartilages are incomplete posteriorly. Connective tissue and involuntary muscle join the cartilages and form the posterior wall where they are incomplete. The soft tissue posterior wall is in contact with the esophagus. The trachea is composed of three layers of tissue:

1. **Outer layer:** The outer layer consists of fibrous and elastic tissue and encloses the cartilage.
2. **Middle layer:** The middle layer consists of cartilage and bands of smooth muscle. There is some areolar tissue, containing blood and lymph vessels and autonomic nerves
3. **Inner layer:** The inner layer or the lumen of the trachea is lined by pseudostratified ciliated columnar epithelium intermingled with goblet cells

Blood Supply

The blood supply to the trachea is through the inferior thyroid and bronchial arteries and the venous return is by the inferior thyroid veins.

Innervation

The trachea is innervated by the parasympathetic and sympathetic nerves. Parasympathetic innervation is by the recurrent laryngeal nerve. The sympathetic innervation is by nerves of the sympathetic ganglia.

Lymphatic Drainage

The lymph from the trachea passes through the lymphatic vessels to the lymph nodes situated around the trachea and in the carnia, the area where it divides into two bronchi.

Bronchi and Bronchioles

The trachea divides into two branches: the right bronchus and the left bronchus. The right bronchus divides into three branches, one to each lobe, after entering the right lung at the hilum. The left bronchus divides into two branches, one to each lobe, after entering the left lung at the hilum.

After entering the lobe each bronchus progressively subdivides into bronchioles, terminal bronchioles, respiratory bronchioles, alveolar ducts, and finally alveoli. The bronchi

are composed of the same tissues as the trachea. They are lined with pseudostratified ciliated columnar epithelium intermingled with goblet cells.

Towards the distal end of the bronchi the cartilages become irregular in shape and are absent at bronchiolar level. In the absence of cartilage the smooth muscles in the walls of the bronchioles become thicker and are responsive to autonomic nerve stimulation. As the bronchus subdivides the pseudostratified ciliated columnar epithelium changes gradually to non-ciliated squamous cells in the alveoli.

Interspersed between the squamous cells are type II alveolar cells (pneumocytes) that secrete surfactant, a phospholipid fluid, which reduces surface tension of the fluid lining the alveoli and prevents the alveolar walls from collapsing during expiration. In addition, surfactant prevents the alveoli from drying out.

Blood Supply

The blood supply to the bronchi and bronchioles is through branches of the right and left bronchial arteries and the venous return is by the right and left bronchial veins.

Innervation

The bronchi and bronchioles are innervated by the parasympathetic and sympathetic nerves. Parasympathetic innervation is by the vagus nerve. The vagus nerve stimulates the contraction of the smooth muscles in the bronchial tree, causing bronchoconstriction, and sympathetic stimulation causes broncho-dilatation.

Lymphatic Drainage

The lymph from the bronchi and bronchioles passes through the lymphatic vessels to the lymph nodes situated around the trachea and bronchial tree and then into the thoracic duct on the left side and right lymphatic duct on the right side.

Lungs

There are two lungs, lying on each side of the midline in the thoracic cavity. They are cone shaped and have an apex, a base, costal surface, and medial surface.

1. **Apex:** The apex is round and rises above the level of the middle third of the clavicle. The structures associated with it are the first rib, and the blood vessels and nerves in the root of the neck
2. **Base:** The base is concave and semilunar in shape and is closely associated with the thoracic surface of the diaphragm
3. **Costal Surface:** The costal surface is convex and is closely associated with the costal cartilages, the ribs, and the intercostal muscles
4. **Medial Surface:** The medial surface is concave and has a roughly triangular shaped area, called the hilum at the level of the 5^{th}, 6^{th}, and 7^{th} thoracic vertebrae. Structures which enter and leave the lung at the hilum include the primary bronchus, the pulmonary artery supplying the lung, the two pulmonary veins draining it, the bronchial artery, the bronchial veins, the lymph vessels, and parasympathetic and sympathetic nerves. The area between the lungs is the mediastinum. It is occupied by the heart, great vessels (inferior vena cava and aorta), trachea, esophagus, right and left bronchi, lymph vessels, lymph nodes, and nerves.

Organization of the Lungs

The right lung is divided into three distinct lobes: superior, middle, and inferior. The left lung is smaller in comparison to the right lung as the heart is situated left to the midline. It is divided

into two lobes: superior, and inferior. Each lobe is made up of large number of lobules.

Pleura and Pleural Cavity

The pleura consist of a closed sac one for each lung, which contains a small amount of serous fluid. The pleura have two layers: one adheres to the lung, and the other to the wall of the thoracic cavity.

1. **Visceral Pleura:** The visceral pleura is adherent to the lung, covering each lobe and passing into the fissures which separate them.
2. **Parietal Pleura:** The parietal pleura is adherent to the thoracic cavity and the thoracic surface of the diaphragm. It is continuous with the visceral pleura at the hilum.

Pleural Cavity

The visceral pleura and the parietal pleura are separated by a space, the pleural cavity. The pleural cavity consists of thin film of serous fluid, which allows the visceral and the parietal pleura to glide over each other, thereby preventing friction between them during respiration.

The two layers of pleura, with the serous fluid between them, behave in the same way as two pieces of glass separated by a thin film of water. They glide over each other easily but can be pulled apart only with difficulty, because of the surface tension between the two glass layers and the water. If either pleura are punctured, the underlying lung collapses due to its inherent elastic property.

Blood Supply

The pulmonary artery divides into two branches, each carrying deoxygenated blood to each lung. Within the lungs each pulmonary artery divides into many branches, which eventually end in a dense capillary network around the walls of the alveoli.

The walls of the alveoli and those of the capillaries consist of only one layer of flattened epithelial cells. The exchange of gases between air in the alveoli and blood in the capillaries takes place across these two thin membranes.

The pulmonary capillaries eventually form two pulmonary veins in each lung. They leave the lungs at the hilum and carry oxygenated blood to the left atrium of the heart. The innumerable blood capillaries and blood vessels in the lungs are supported by connective tissue.

ASTHMA

Asthma is an inflammatory disease of the bronchioles in which the mucous membranes and muscle layers of the bronchioles become thickened and the mucous glands present in the submucosa enlarge, reducing airflow in the lower respiratory tract. The airway is obstructed during an asthmatic attack due to spasmodic contraction of bronchial muscles (bronchospasm) and excessive secretion of mucous.

An attack of asthma is characterized by severe dyspnoea and wheezing (soft whistling sound during expiration). Inspiration is normal but only partial expiration is achieved, resulting in hyperinflation of the lungs due to air trapped distal to the bronchi, where the bronchioles are constricted and filled with mucous and debris.

The duration of attacks usually varies from a few minutes to hours, and very occasionally, days (status asthmaticus). In severe acute attacks the bronchioles may be obstructed by mucous plugs, leading to hypoxia, hypercapnia (high level of carbon dioxide in the circulating blood), acidosis, and possibly death.

With good management the symptoms may diminish and even disappear, allowing the patient to lead a normal professional and social life. Asthma is most commonly found in children, with about half of all cases developing before the age of 10 years. However, up to 70 percent of

children with asthma undergo remission by the age of 20 years.

Definition

The definition of asthma proposed by the International Consensus and by the "Global Strategy for Asthma Management and Prevention" is as follows:

"Asthma is a chronic, inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment."

Risk Factors

The risk factors, which may trigger an asthmatic attack include:

1. **Hereditary:** Heredity is also a predisposing factor in asthma, and a family history of asthma is common among asthma patients.
2. **Allergy:** Allergy is the most important predisposing factor in asthma. It is reflected in the tendency to produce abnormally high levels of immunoglobulin E (IgE) in response to exposure to allergens in the environment. Some of the allergens include dust mites, animals (cats, dogs, rats, cockroaches etc.), moulds (a fungus that produces a superficial growth on various kinds of damp or decaying organic matter), pollen, and food.
3. **Environmental:** Environmental factors include dust, tobacco smoke, cold air, air pollution, upper respiratory tract infection, stress, and strenuous exercise.

Pathogenesis

An understanding of the mechanism by which asthma develops provides the basis for the methods of treatment currently proposed for its management. Asthma is considered to be caused by many factors in individuals who often have a genetic tendency towards the disease.

The pathogenesis of extrinsic asthma is readily explained by type 1 hypersensitivity reaction. However, the pathogenesis of intrinsic asthma is non-immune and is unknown or poorly defined.

Inhalation of allergens stimulates the production of immunoglobulin E (IgE) antibodies that bind to the surface of mast cells in the airways (bronchioles). When the allergen is encountered again, the antigen and antibody reaction results in the release of histamine and other mediators (leukotrienes, prostaglandins, platelet activating factor, and mast cell tryptase) from the mast cells, that open tight junctions between pseudostratified columnar ciliated cells. Antigen then enters the submucosa to activate more mast cells and eosinophils, which in turn release chemical mediators which induce bronchoconstriction, bronchospasm (Fig.12.9), vasodilatation, increased vascular permeability, and increased mucous production.

Classification

Asthma is commonly classified as extrinsic and intrinsic. However, both give rise to identical symptoms and are treated in the same way. Important differences include age of onset and contribution of allergens. The distinction between these two types of asthma is largely academic, because in clinical practice, many patients do not fit into either category but instead fall into a mixed group with features of each.

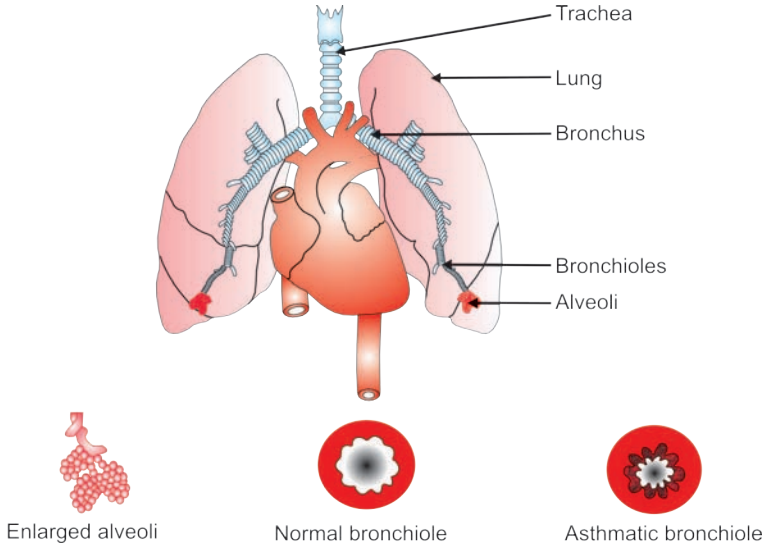

Fig. 12.9: Structure of lungs and asthmatic bronchiole

Extrinsic Asthma (Childhood Onset, Allergic, Atopic Asthma)

The extrinsic asthma occurs in children and young adults who are atopic, that is, they readily develop IgE antibodies against allergens (Type I hypersensitivity). Attacks tend to become less frequent and less severe with age.

Intrinsic Asthma (Adult Onset, Late Onset, Cryptogenic Asthma)

The intrinsic asthma occurs later in adult life and there is no history of childhood allergic reactions. These patients are said to have a predisposition to asthma (asthmatic diathesis). In intrinsic asthma, the factors responsible for attacks are unknown or poorly defined. However, some of the factors responsible for attacks include: aspirin, penicillin, nasal polyps, chronic bronchitis, cold, psychological stress, exercise, and inhaled irritants such as ozone, nitrogen dioxide, and sulfur dioxide. Attacks tend to increase in severity and there may be irreversible damage to the lungs. Eventually impaired lung function (ventilation) leads to hypoxia, pulmonary hypertension, and right-sided heart failure.

Clinical Symptoms

The principal clinical symptoms of asthma are:

1. Wheezing
2. Chest tightness
3. Dyspnea (breathlessness)
4. Cough

However, none of these clinical symptoms is specific for asthma, and may occur with other chest conditions. As a result, asthma is often misdiagnosed and therefore poorly treated, or even not treated at all. Asthma must always be considered in case of the following:

1. Episodes of breathlessness occur mainly at nights that wake up the patient, especially in the early hours of the morning
2. Breathlessness compels the patient to sit up in bed to relieve the symptoms
3. The patient has a history of coughing spells
4. The symptoms appear in recurrent attacks
5. The symptoms disappear either spontaneously or after taking asthma medication (bronchodilator)
6. The patient has a personal or family history of allergic reactions

7. Symptoms are brought on by a variety of factors such as dust, cold air or strenuous exercise or stress

Diagnosis

Before treating a patient for asthma, it is necessary to:

1. Establish the diagnosis of asthma and identify the possible causal and trigger factors
2. Determine the degree of severity of the disease

If the patient has already been examined during an attack, the diagnosis is obvious. Diagnosis is more difficult if the patient presents during symptom free period.

History

Case history taking is the key to diagnosis. In taking the history it is important to use simple words, in a manner that is easy for the patient to understand (or the family, if the patient is a child). Open questions are asked to allow the patient or family to provide information about the history of the disease, and specific questions to obtain information about the respiratory symptoms, time of attacks, variability (recurrence) of attacks, trigger factors, as well as factors that improve the symptoms. Recurrent attacks of breathlessness, mainly at night, with wheezing, that wake the patient and compels the patient to sit up to be able to breathe, are the symptoms most characteristic of asthma.

Clinical Examination

If the patient presents during a symptom free period, the results of the clinical examination often do not lead to a diagnosis of asthma. The presence of wheezing is consistent with asthma; however, wheezing is not specific for asthma, and may occur with other chest conditions. The presence of crackles is suggestive of other conditions. Nevertheless, the absence of wheeze does not exclude asthma, as during symptom free periods there is no evident abnormality and the auscultation is normal.

Chest Radiograph

Although chest radiograph has no place in the diagnosis of asthma, it is, nevertheless, used:

1. If conditions other than asthma are suspected that are likely to cause the symptoms mentioned by the patient
2. If a complication of asthma is suspected, such as pneumothorax or pneumonia

Lung Function Tests

Lung function tests should be conducted for all persons suspected of having asthma. The diagnosis is confirmed by measurement of peak expiratory flow (PEF) using a simple peak flow meter or spirometry.

Peak Flow Meter

The peak flow meter is a tool that is reliable, robust, practical and cheap, used to detect airflow limitation. The degree of airflow limitation can be evaluated by comparing the patient's PEF level with the 'normal' value of PEF expected. Predicted or 'normal' values of PEF are given in tables by age, sex and height for adults and by height only for children.

Spirometry

Spirometry is another method used to test lung function and for both diagnosis and assessment of progress. Spirometry is the method of choice as measurement of PEF by peak flow meter has significant limitations, but in most low or middle income countries it is only available in large hospitals and some specialized referral centers. The aim of spirometry is to:

1. Diagnose airflow obstruction
2. Measure the degree of airflow obstruction
3. Monitor the effects of treatment
4. Demonstrate the presence of airflow obstruction to the patient
5. Demonstrate the presence of reversibility of airflow obstruction to the patient
6. Provide objective feedback to the patient about the presence and severity of asthma

Treatment

Objectives of Treatment

The treatment objectives should be explained to the patient and/or the patient's family from the start of treatment. It should also be explained that treatment is long term and that it is impossible to determine immediately how long it will take to attain these objectives. Asthma is under control when the following objectives are reached:

1. **Clinical Objectives**
   a. Reduction and even total disappearance of symptoms, particularly nocturnal
   b. Absence of visits to the physician
   c. No limitation of day-to-day activities
2. **Functional Objective**
   Peak expiratory flow (PEF) normal or > 80% of PEF predicted
3. **Treatment Objective**
   a. No need or only occasional need to use bronchodilator
   b. In the most severe and persistent cases, these objectives may not be achieved due to irreversible inflammatory changes of the bronchial mucosa. The objectives of treatment are modest:
      i. Clinical and functional improvement
      ii. Trying to obtain the best results possible with the minimum of side effects
4. **Preventive Measures**
   Preventive measures consist of avoiding or controlling the risk factors of asthma and parents of children with asthma should be informed that it is harmful to expose their child to passive smoking

ESSENTIAL DRUGS FOR TREATMENT OF ASTHMA

To manage asthma patients, the drugs must always be available. A limited number of drugs are necessary for long-term treatment of asthma and are included in the WHO list of essential drugs (Table 12.10).

Corticosteroids

Inhaled Corticosteroids (beclomethasone)

Because of its effectiveness and low rate of side effects, inhaled beclomethasone in high doses, is the treatment of choice for cases of persistent asthma. Due to its anti-inflammatory action, it progressively reduces bronchial inflammation and thereby the symptoms of asthma.

Local side effects include hoarseness, mild sore throat, and oropharyngeal candidal infection, if daily treatment consists of doses >1000 µg. These side effects can be avoided by advising patients to use a large volume spacer and to rinse and gargle with water after use of their inhaler.

Table 12.10: Essential drugs for asthma treatment

Type of drug	*Generic name*	*Mode of administration and dosage*
Corticosteroids	Beclomethasone	Aerosol (inhaler): 250 µg per puff
	Prednisolone	Tablets: 4-5 mg
Bronchodilator	Salbutamol	Aerosol (inhaler): 100 µg per puff

Systemic Corticosteroids (Oral prednisolone)

These can be used in short or long-term treatment:

1. **Short-term:** They are used to treat acute attacks for a short period, and then stopped. In this case they have few or no harmful side effects.
2. **Long-term:** Due to their harmful effects, they should only be used for severe persistent asthma or status asthmaticus, which do not respond to other treatments. Harmful effects of long-term corticosteroids include infections (in particular tuberculosis), diabetes mellitus, hypertension, and osteoporosis. Furthermore, acute adrenal insufficiency can occur if long-term oral corticosteroids are suddenly interrupted.

Bronchodilators

These drugs aim to reduce bronchospasm caused by an allergen-induced immune response. Three groups of drugs are included:

1. β_2-agonists (drugs that can combine with a receptors on a cell to produce a physiological reaction)
2. Muscarinic receptor antagonists (drugs that neutralizes or counteracts the effects of another drug)
3. Methylxanthines

β_2-agonists

β_2-agonists are the most powerful bronchodilators. They relax the bronchial smooth muscle and assist in clearing the mucus secretions present in the bronchial airways. β_2-agonists are broadly classified as short acting and long acting. The long acting β_2-agonists such as salmeterol and formoterol exert an effect within 10-20 minutes and can be maintained for up to 12 hours.

Short acting β_2-agonists are the drugs of choice for asthma attacks and for preventing exercise induced asthma. Short acting β_2-agonists initiate a bronchodilator effect within 15-19 minutes and can be maintained for up to 6 hours. They are well-tolerated and systemic side effects (tachycardia, tremors, and hypokalaemia), which may result from large doses is rare. Salbutamol is one of the best short-acting β_2-agonist. Administration is preferably by inhalation, due to the following reasons:

1. Small doses
2. Rapid action (attaining its maximum action in a few seconds)
3. Almost total absence of side effects

β_2-agonists such as salbutamol and terbutaline can produce xerostomia, dysgeusia, and discoloration of the teeth. Dry mouth may increase incidence of dental caries and thus a prophylactic regimen is important. If the dry mouth is severe, lubrication with saliva substitutes may be indicated. The hypokalaemia which may result from large doses of β_2-agonists may be aggravated by high doses of corticosteroids and by adrenaline in used in dental local anesthetics.

Muscarinic Receptor Antagonists

Muscarinic receptor antagonists (anticholinergic) to reverse the effects of acetylcholine released from vagus nerve. The aim of muscarinic receptor antagonists is to cause bronchodilatation by acting as antagonists of acetylcholine for muscarinic receptors (macaronis M 2- M5 subtypes) located in smooth muscle cells of bronchioles.

The two examples of muscarinic receptor antagonists used to treat airway hyperresponsiveness are ipratropium and oxitropium bromide. It has additive bronchodilator effect with theophylline and therefore is more effective in chronic obstructive pulmonary disease (COPD) than in bronchial asthma. Transient side effects include xerostomia, dysguesia, blurred vision, and

urinary retention. Systemic side effects are rare because of poor absorption from lungs.

Methylxanthines

The two drugs that are commonly used in this group are theophylline and aminophylline and they produce actions similar to that of caffeine. Theophylline and aminophylline are the second most common drugs used in the treatment of asthma.

Dental Considerations

1. Effort should be made to relieve anxiety as far as possible.
2. Treatment should not be carried out if the patient has not brought their normal medication and if such medication is unavailable.
3. Patients may not be comfortable in the supine position.
4. If possible, asthmatic patients should be treated using local anesthesia.
5. General anesthesia using nitrous oxide and oxygen is preferred to intravenous sedation since the former can be rapidly controlled.
6. General anesthesia can be complicated by hypoxia and increased carbon dioxide which can lead to pulmonary oedema even if cardiac function is normal.
7. Nonsteroidal anti-inflammatory drugs should not be prescribed as many asthmatic patients are allergic to these analgesics. Similarly, sulphite-containing compounds (such as preservatives in some adrenaline containing local anesthetics) can produce allergy in asthmatic patients.
8. A severe asthmatic attack can be life threatening and stress during dental treatment procedures may contribute to the beginning of such a condition and therefore the dentist should have the equipment to deal with such an emergency. In case of an emergency:
   a. A salbutamol inhaler or nebulised salbutamol is useful.
   b. Intravenous aminophylline (250-500 mg by slow IV injection over 20 min) is reserved for patients who do not respond quickly to nebulised salbutamol.
   c. Intramuscular or intravenous prednisonlone (4-60 mg) should be administered to all severely ill patients.
   d. Intramuscular chlorpheniramine maleate (10-20 mg) or intravenous chlorpheniramine maleate (10-20 mg slow IV injection over 1 min) or should be administered for the management of anaphylactic shock.

III. DIABETES MELLITUS AND DENTAL CARE

Diabetes mellitus is a chronic metabolic disorder characterized by disorders of carbohydrate, protein and lipid metabolism, resulting in hyperglycemia.

Islets of Langerhans

The pancreas consist groups of cells called islets of Langerhans which secrete their hormones directly into the blood. The different cells types are as follows:

1. α cells which secrete glucagon
2. β cells which secrete insulin and amylin
3. δ cells which secrete somatostatin
4. PP cells which secrete pancreatic polypeptide

Classification

Type 1 or insulin dependent diabetes mellitus (IDDM) or juvenile

1. Type 2 or non-insulin dependent diabetes mellitus (NIDDM) or maturity onset
2. Gestational diabetes mellitus
3. Drug induced diabetes mellitus
4. Diabetes mellitus due to infections
5. Diabetes mellitus associated with syndromes

Normal Glucose Metabolism

In a normal person the blood glucose level is < 110 mg/dl. But after consumption of meals it increases to 120-140 mg/dl. The blood glucose level returns to normal within 2 hours, this is achieved by secretion of insulin by the β cells of islets of Langerhans. To carry out its effects insulin first binds with its receptor and activates the cell membrane, facilitating the entry of glucose into cell. The insulin receptor consists of four subunits (two α subunits and two β subunits) held together by disulfide bonds. Most of the receptors are present in the muscle tissue. When the blood glucose level decreases, α cells of islets of Langerhans secrete glucagon which breakdowns the liver and muscle glycogen (glycogenolysis) and proteins (gluconeogenesis) to increase the blood glucose levels.

Type 1 Diabetes Mellitus

It comprises approximately 3-5% of all cases of diabetes mellitus and is usually seen in people below 40 years. The various etiological factors of type 1 diabetes mellitus are:

1. Autoimmune related destruction of â cells of islets of Langerhans (Fig.12.10) leading to deficiency in insulin and increased blood glucose levels
2. Genetics (HLA–DR3) also plays an important role in the development of type 1 diabetes mellitus

Type 2 Diabetes Mellitus

It accounts for 95% of all cases of diabetes mellitus and usually affects people who are above 40 years when the basal metabolic rate is low. But there is a recent trend which shows that type 2 diabetes mellitus also affects people who are in the age group of 20 years, which is related to truncal obesity and lack of exercise. Obesity increases insulin levels and decreases the concentration and sensitivity of insulin receptors. Therefore glucose uptake is very minimal at the cellular level resulting in hyperglycemia. However, exercise and modified lifestyle increases the concentration and sensitivity of insulin receptors.

Clinical Features

The classical clinical features of diabetes mellitus (Fig.12.11) are as follows:

1. Polyuria (increased diuresis)
2. Polyphagia (increased appetite)
3. Polydipsia (increased thirst)
4. Asthenia (weakness due to loss of muscle mass)

Gestational Diabetes Mellitus

During the third trimester of pregnancy there is diabetes mellitus. However, after parturition the blood glucose levels return to normal. The various mechanisms that lead to gestational diabetes are:

1. Increased absorption of glucose from gastrointestinal tract
2. Inability of insulin to convert glucose into glycogen
3. Impaired tubular reabsorption of glucose, which leads to glycosuria

Drug or chemically Induced Diabetes Mellitus

There are many drugs or chemicals that induce diabetes mellitus few of them are:

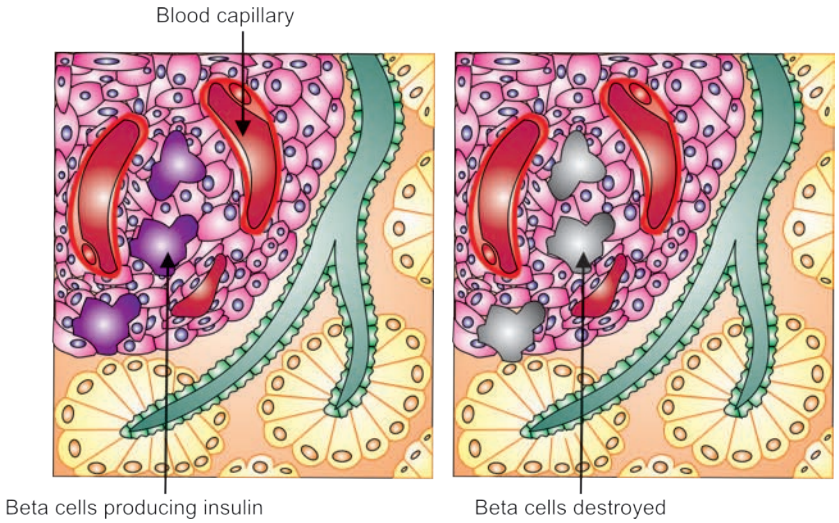

Fig. 12.10: IDDM diabetes mellitus

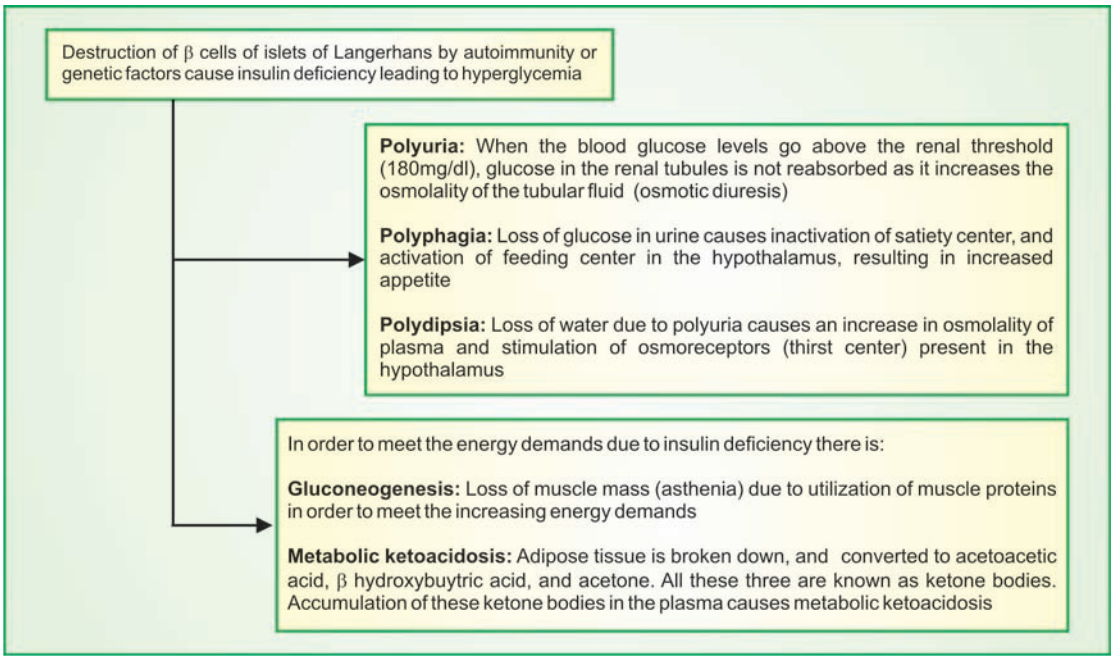

Fig. 12.11: Clinical features of diabetes mellitus

1. Thyroxine or T_4
2. Thiazide diuretic e.g., chlorothiazide
3. Glucocorticoids
4. Phenytoin sodium
5. α-interferon

Diabetes Mellitus due to Infections

1. Congenital rubella
2. Cytomegalovirus virus

Diabetes Associated with Syndromes

1. Down's syndrome
2. Turner's syndrome
3. Klinefelter's syndrome
4. Grinspan syndrome

COMPLICATIONS

Increased Susceptibility to Infection

Diabetics are prone to bacterial, viral and fungal infections because of:

1. Hyperglycemia
2. Diabetic microangiopathy

Hyperglycemia

A consequence of hyperglycemia in diabetes mellitus is the alteration of circulating and immobilized proteins. When proteins such as collagen, or lipids, are exposed to aldose sugars, they undergo nonenzymatic glycosylation or glycation. Initially the nonenzymatic glycosylation of proteins is reversible, but eventually the nonenzymatic glycosylation of proteins becomes irreversible and irreversible glycosylated proteins are formed.

These irreversible glycosylated proteins are called advanced glycosylation end products (AGEs). The AGEs accumulate in high levels in the tissues, including the periodontium. AGEs induce marked changes in the cells (fibroblasts) and extracellular matrix components (glycosylation of existing collagen at the wound margins results in delayed remodelling at the wound site).

The accumulation of AGEs in the tissues of patients with diabetes mellitus also increases the intensity of the inflammatory response to periodontal pathogens, because inflammatory cells such as monocytes and macrophages have receptors for AGEs. Interactions between AGEs and their receptors (RAGEs) on inflammatory cells result in the increased production of matrix metalloproteinases, proinflammatory cytokines such as IL-1β, IL-6, and mediators such as TNF-α. This interaction may be the cause of increased levels of IL-1β, IL-6, and TNF-α in the gingival crevicular fluid and may magnify the inflammatory response, alter wound healing, and induce connective tissue damage, and bone resorption.

Diabetic Microangiopathy

Diabetics have a predisposition to develop vascular lesions of the small blood vessels (arterioles, capillaries, and venules). Diabetic microangiopathy is characterized by deposition of proteins at the basement membrane, which ultimately leads to thickening of the basement membrane and finally vascular occlusion. Diabetic microangiopathy affects several organ systems and the lesions are seen in the retina (retinopathy), kidneys (nephropathy), and peripheral nerves (neuropathy). Diabetic microangiopathy interferes with the delivery of nutrients and adherence, chemotaxis, and phagocytosis of PMNL to the tissues, resulting in decreased oxygen supply and elimination of metabolic waste, contributing to altered wound healing and periodontitis. The vascular changes worsen with poor metabolic control and longer duration of the disease.

Altered Wound Healing

Altered wound healing is a common problem in diabetics due to diabetic microangiopathy, improper function of primary reparative cell

(fibroblast) due to hyperglycemia, and degradation of collagen by matrix metalloproteinase enzymes, the production of which is elevated in diabetes mellitus. Thus, periodontal wound healing in response to chronic microbial insult may be altered in uncontrolled diabetes mellitus, resulting in increased bone loss and attachment loss.

Metabolic Ketoacidosis

As blood glucose is not utilized by the cells due to severe deficiency of insulin, large amounts of adipose tissue is broken down (lipolysis) for release of energy leading to circulation of free fatty acids in the blood and resultant metabolic ketoacidosis or diabetic ketoacidosis (DKA). Also, the inhibitory effect of lipase is withdrawn due to severe insulin deficiency. The signs and symptoms of metabolic ketoacidosis include nausea, disorientation, abdominal cramps, and fatigue.

Hypoglycemic Shock

Hypoglycemia is characterized by sweating (diaphoresis), confusion, tremors, tachycardia, and permanent brain damage. Hypoglycemic signs and symptoms are likely to occur if the blood glucose level falls below <60 mg/dl. The most common causes of hypoglycemia include:

1. Injection of excess insulin
2. No caloric intake with the usual dose of insulin
3. Increasing exercise without adjusting insulin dose (exercise reduces the requirement of insulin)
4. Alcohol intake (alcohol inhibits gluconeogenesis)

Atherosclerosis Leading to Myocardial Infarction

The cause of atherosclerosis in Type 1 and 2 diabetes mellitus is due to hyperlipidemia.

Diabetic Neuropathy

Diabetic neuropathy is characterized by segmental demyelinization, and injury to Schwann cells.

Diabetic Retinopathy

Diabetic retinopathy is due to diabetic microangiopathy and is the leading cause of blindness in diabetes mellitus.

Diabetic Nephropathy

Kidneys are commonly involved in diabetes mellitus and the various types of lesions associated with diabetic nephropathy are:

1. **Diffuse glomerulosclerosis:** Thickening of basement membrane of glomerular vessels
2. **Nodular glomerulosclerosis:** Focal deposition of hyaline in the lobule of glomerulus (Kimmelsteil-Wilson lesions)

Diagnosis

An International Expert Medical Committee was established in May 1995 to renew the scientific literature since 1979 and to decide the changes to the classification and diagnosis of diabetes mellitus if needed.

The International Expert Medical Committee recommended the new revised diagnostic criteria for diabetes mellitus from those recommended by National Diabetes Data Group (NDDG) and WHO, which was based on type of pharmacological treatment used in the management of diabetes mellitus.

Criteria for the Diagnosis of Diabetes Mellitus

1. Classical symptoms (polyuria, polyphagia, polydipsia, and asthenia)
2. Casual plasma glucose concentration ≥ 200 mg/dl (casual means anytime of the day without regard to time since last meal)

3. Fasting plasma glucose (FPG) ≥ 126 mg/dl (fasting is defined as no caloric intake for at least 8 hours)
4. Two hours postprandial glucose ≥ 200 mg/dl during an oral glucose tolerance test (OGTT). According to WHO this test has to be performed by giving 75 gm anhydrous glucose dissolved in water
5. In absence of any hyperglycemia these tests have to be carried out on different day.

The expert committee has recognized an intermediate group of subjects whose glucose levels are not meeting the criteria for diabetes mellitus. The glucose levels of this intermediate group of subjects are too high to be considered normal but too less to be considered as diabetes mellitus. This intermediate group of subjects have impaired fasting plasma glucose (IFG) levels ≥ 110 mg/dl but ≤ 126 mg/dl. The categories of FPG are as follows:

1. FPG < 110 mg/dl = Normal fasting plasma glucose
2. FPG ≥ 110 and ≤ 126 mg/dl = Impaired fasting plasma glucose (IFG).
3. FPG ≥ 126 mg/dl = Provisional diagnosis of diabetes mellitus

The corresponding categories when OGTT is used are as follows:

1. Two hours postprandial glucose < 140 mg/dl = Normal glucose tolerance test
2. Two hours post-prandial glucose ≥ 140 mg/dl and ≤ 200 mg/dl = Impaired glucose tolerance test (IGT)
3. 2 hours post prandial glucose ≥ 200 mg/dl = Provisional diagnosis of diabetes mellitus.

Diagnostic Tests

Blood Analysis

1. Casual blood glucose (casual means anytime of the day)
2. Fasting blood glucose
3. Gluostix reagent strips for blood glucose monitoring

Urine Analysis

1. Benedicts test
2. Diastix reagent strips for urine glucose monitoring
3. Keto-diastix reagent strips for diagnosis of ketone bodies and glucose in urine

Oral Glucose Tolerance Test

- Two hours postprandial glucose test.

Monitoring Diabetes Mellitus

Glycosylated Hemoglobin Assay

Glycosylated or glycated hemoglobin assays have emerged as the "gold standard" for long term glycemic control. It assesses the glycemic control and has a prognostic value as it was shown in the diabetes control and complications trial in 1993. Glycosylated hemoglobin assay cannot be influenced by recent caloric intake. Glycosylation or glycation is the nonenzymatic reaction of glucose with the hemoglobin A molecule within the circulating erythrocytes resulting in the formation of glycosylated hemoglobin (HbA_{1C}). This test measures the glucose that binds to hemoglobin A molecule within the circulating erythrocytes and remains attached for the life span of the RBC (120 days). Therefore, the levels of glycosylated hemoglobin indicate the glycemic state over a period of 8 to 12 weeks. Reduced glycosylated hemoglobin levels decreases the incidence of diabetic mellitus complications. The normal value of glycosylated hemoglobin is less than 6%. Glycosylated hemoglobin levels above 8% indicate the existence of higher levels of plasma glucose.

Fructosamine Test

The principle behind this test is that glucose reacts with serum proteins to produce fructosyl derivative called fructosamine. The concentration of fructosamine increases over a period of time and is helpful in controlling diabetes

mellitus. Fructosamine test is a marker of glycemia over the preceding 2 to 3 weeks.

Treatment of Diabetes Mellitus

Type 1

Type 1 diabetic patients need exogenous source of insulin. Insulin was first discovered by Banting and Best. The most common complication of insulin therapy is hypoglycemia. The various types of insulin are as follows:

1. **Short acting:** Regular insulin
2. **Rapid acting:** Insulin aspart, lispro
3. **Intermediate acting:** Neutral protamine hagedron (NPH) and lente (most effective treatment)
4. **Long acting:** Ultralente and new developed suspension free insulin (glargine)

Insulin can be administered using a traditional insulin syringe, an insulin pen or a subcutaneous insulin pump or SCII.

Insulin pump

It is a battery powered device that delivers phosphate-buffered rapid or short acting insulin stored in a reservoir syringe that is located within the plastic pump and is replaceable. If the insulin is not buffered, then it may precipitate (separate as a fine suspension of solid particles) inside the system, resulting in occlusions that can stop the flow of the insulin.

Insulin is delivered from the device by means of an infusion set. The infusion set consists of a plastic tube (the catheter) with a plastic or metallic needle. The needle is inserted subcutaneously into upper arm, abdomen or thigh. Patient has to replace the infusion set every 48 hours to avoid infection at the site of insulin delivery.

The major risk associated with the insulin pump is the rapid development of severe hyperglycemia and metabolic ketoacidosis, leading to diabetic coma. The insulin pump controls the blood glucose levels through a finely tuned glucose control program. The insulin pump can deliver incremental doses as low as 0.1 unit of insulin/hour. The lowest dose that a patient can deliver with accuracy through a traditional syringe is 1.0 unit.

However, if there is mechanical disruption of this finely tuned glucose control program, counter regulatory hormones to insulin, such as adrenaline (increases glycogenolysis) and glucocorticosteroids (increases gluconeogenesis) cause hyperglycemia. Metabolic ketoacidosis is another risk associated with insulin pump, therefore patients using insulin pump generally carry back-up supplies of insulin and insulin syringes in case there is a mechanical problem with the insulin pump.

Type 2

Most of the patients suffering from Type 2 diabetes mellitus can control hyperglycemia by reducing weight either by diet control or exercise. Exercise increases the concentration and sensitivity of insulin receptors and reduces the requirements of exogenous insulin. Most of the oral hypoglycemics cause hypoglycemia. Oral hypoglycemics are of no use in Type 1 diabetes mellitus. The oral hypoglycemic agents are classified as follows:

1. **α-glucosidase inhibitors**: Acarbose, miglitol (block the absorption of carbohydrate in small intestine leading to hypoglycemia)
2. **Sulfonylureas:** (increase the secretion of insulin from the β cells)
   a. First generation—Tolbutamide, chlorpropamide
   b. Second generation—Gilbenclamide, Glipizide
3. **Biguanides:** Metformin and phenformin (enhance binding of insulin to its receptors)
4. **Thiazolidin-ediones:** Rosiglitazone, pioglitazone (increase tissue sensitivity to insulin, especially in muscle)

5. **Benzoic acid derivatives:** Repaglinide, nateglinide (increase the secretion of insulin from the â cells)

ACE Inhibitors

It was recently found out that angiotensin converting enzyme inhibitor ramipril decreases the incidence of diabetes mellitus related complications. Ramipril is an antihypertensive drug. The side effect of ramipril includes sudden swelling of lips, tongue, face and laryngeal tissues leading to asphyxia. Adrenaline 1:1000 can be administered to overcome this side effect.

Oral Manifestations of Diabetes Mellitus

Oral manifestations of diabetes mellitus are due to:

1. Hyperglycemia
2. Diabetic microangiopathy
3. Polyuria leading to xerostomia

Oral Manifestations

1. Xerostomia
2. Dental caries
3. Gingivitis
4. Periodontitis
5. Dysphagia
6. Candidosis
7. Recurrent aphthous ulcers
8. Lichen planus
9. Burning mouth syndrome
10. Glossodynia
11. Dysesthesia (impairment of sensation short of anesthesia)
12. Dysguesia (impairment in the sense of taste)

Dental Management

To avoid complications in a dental chair the following precautions are to be taken by the dental surgeon prior to starting of the treatment:

1. The dentist should know the time, dose and type of insulin the patient has taken, which is possible through a detailed case history.
2. Treatment should be done under antibiotic coverage.
3. Physician's approval whether the diabetic is fit for treatment.
4. Dentist should keep a glucometer with him and check the blood glucose level prior to the treatment.
5. The dentist must be aware of the signs and symptoms of hyperglycemia and metabolic ketoacidosis. He should ensure that the plastic tube from the insulin pump is not compressed by the dental chair because this will block the flow of insulin.
6. The treatment should not be stressful.
7. Just prior to treatment the dentist should check the blood glucose level with a glucometer.
   a. If the glucometer shows blood glucose levels below 80 to 120 mg/dl then a glucose or fruit juice can be administered. Also dissolved sugar placed sublingually may reverse hypoglycemia as the dissolved sugar is rapidly absorbed from the sublingual site. However, if the patient is sedated then 25 to 30 ml of 10% dextrose or 1 mg of glucagon can be administered intravenously, intramuscularly, or subcutaneously. Glucagon causes glycogenolysis and reverses hypoglycemia usually within 15 minutes.
   b. However, if the glucometer shows severe hyperglycemia (> 400 mg/dl) the dentist should call upon the physician immediately. The physician may instruct the dentist to administer rapid acting insulin with an insulin syringe. In a patient using insulin pump, the insulin injection is administered after disconnecting the insulin pump. Finally the dentist should call an ambulance or refer the patient for immediate medical care.

IV. BELL'S PALSY

The Motor Pathway

The motor pathway comprises two major neurons: upper motor neuron and lower motor neuron (Fig.12.12).

Upper Motor Neuron

The cell bodies of this neuron are usually located in the cerebral cortex. Its axon projects caudally and bilaterally to contact the cell bodies of the lower motor neurons in the brain stem (pons).

Lower Motor Neuron

The cell bodies of this neuron are usually located in the brain stem. The cell bodies of the lower motor neurons form motor group of cranial nerve nuclei. Axons that leave these nuclei make up the lower motor neurons.

Facial Nerve

Knowledge of the anatomy of the facial nerve is important in understanding the pathophysiology and management of Bell's palsy. The various components of the facial nerve are: (i) Branchial motor, (ii) Visceral motor, (iii) General sensory and (iv) Special sensory. The branchial motor component constitutes the largest part of the facial nerve fibers. The remaining fibers *(visceral motor, general sensory and special sensory)* are bound in a distinct fascial sheath and are referred to as nervus intermedius. The functions of various components of facial nerve are as follows:

1. **Branchial motor:** To innervate the stapedius, stylohyoid, posterior belly of digastric, occipitalis, muscles of facial expression, and platysma.
2. **Visceral motor:** For stimulation of lacrimal, sub-mandibular, and sublingual glands as well as mucous glands in the nasal mucosa, hard and soft palate
3. **General sensory:** To innervate the skin of the concha of the auricle, and a small area behind the ear
4. **Special sensory:** To carry taste sensation (salty, sweet, sour, and bitter) from taste buds

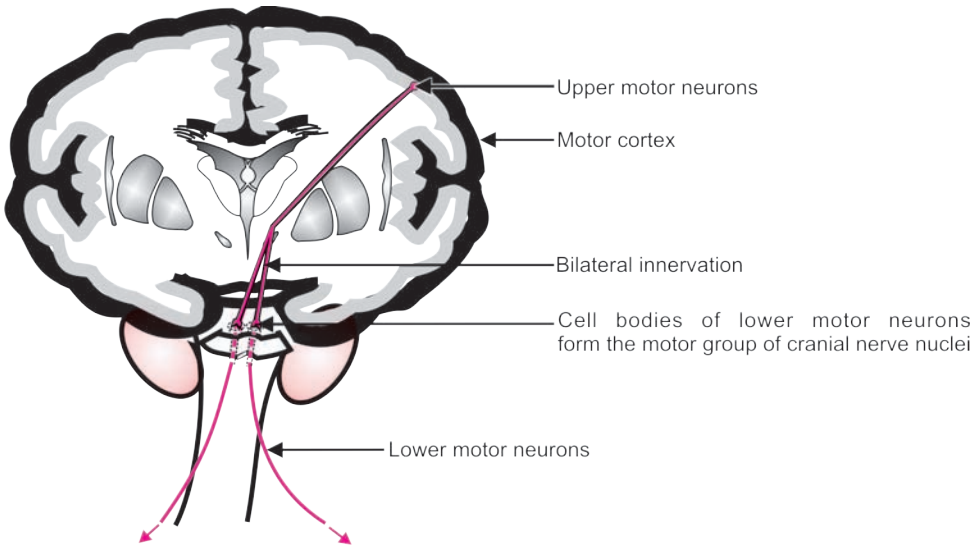

Fig. 12.12: The motor pathway

on the lateral border of the anterior two-third of the tongue

The corticobulbar axons (upper motor neurons) that arise from the motor cortex of the cerebral hemispheres carry signals for voluntary movement of the facial muscles. The corticobulbar axons then travel through the posterior limb of the internal capsule, to reach the ipsilateral and contralateral motor nuclei of the facial nerve present in the brainstem (Fig.12.13).

Fibers that project to the part of the nucleus that innervates the upper muscles of facial expression project bilaterally. Fibers that project to the part of the nucleus that innervates the lower facial muscles of facial expression project only contralaterally (Fig.12.14).

The lower motor neuron (facial nerve) courses dorsally towards the floor of the fourth ventricle and loops around the abducens nucleus to form a slight bulge, the facial colliculus. The loop around the abducens nucleus is the internal genu of the facial nerve. The facial nerve then turns ventrally to emerge from the ventrolateral aspect of the pons, to enter the temporal bone *via* internal auditory meatus along with vestibulocochlear nerve (Fig.12.14). The segment of the facial nerve within the internal auditory meatus is the meatal segment.

The meatal segment of the facial nerve remains in the internal auditory meatus and enters the facial canal or fallopian canal at the meatal foramen. The meatal foramen (mean diameter 0.68 mm) is the narrowest part of the facial canal. Therefore, the meatal foramen constitutes a "physiologic bottleneck" in the presence of neural edema. The facial nerve is without epineurium in the meatal foramen and is instead ensheathed by periosteum.

The labyrinthine segment of the facial nerve, encased within the meatal foramen of the facial canal courses 2-4 mm laterally and takes an acute turn to enter the middle ear. This acute turn is called the genu and is thickened by the presence of the geniculate ganglion (Fig.12.15). The geniculate ganglion is so called because it lies on the genu.

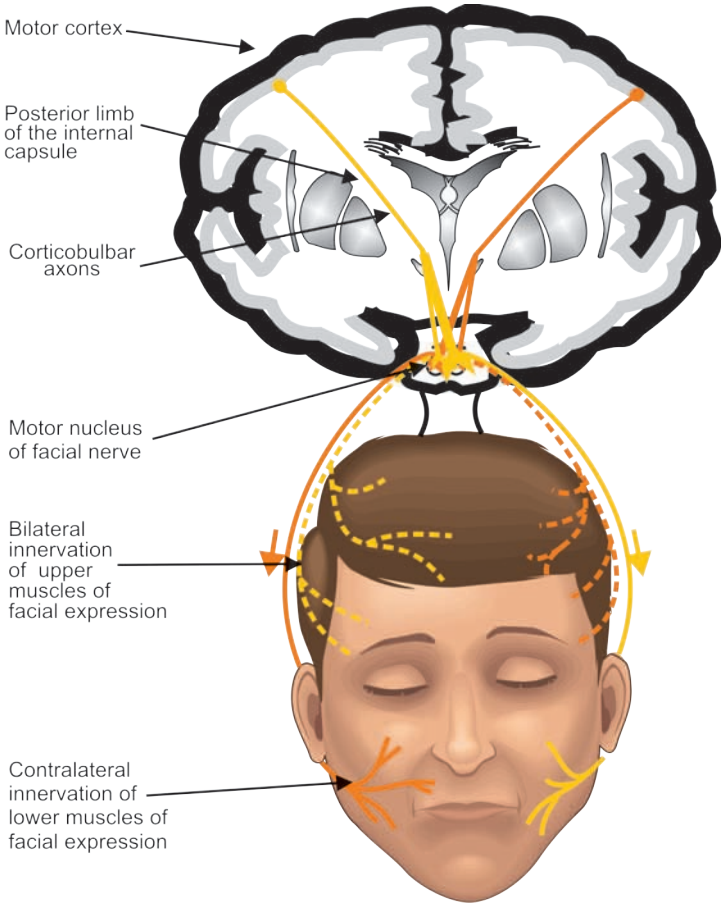

Fig. 12.13: Bilateral and contralateral nerve projection

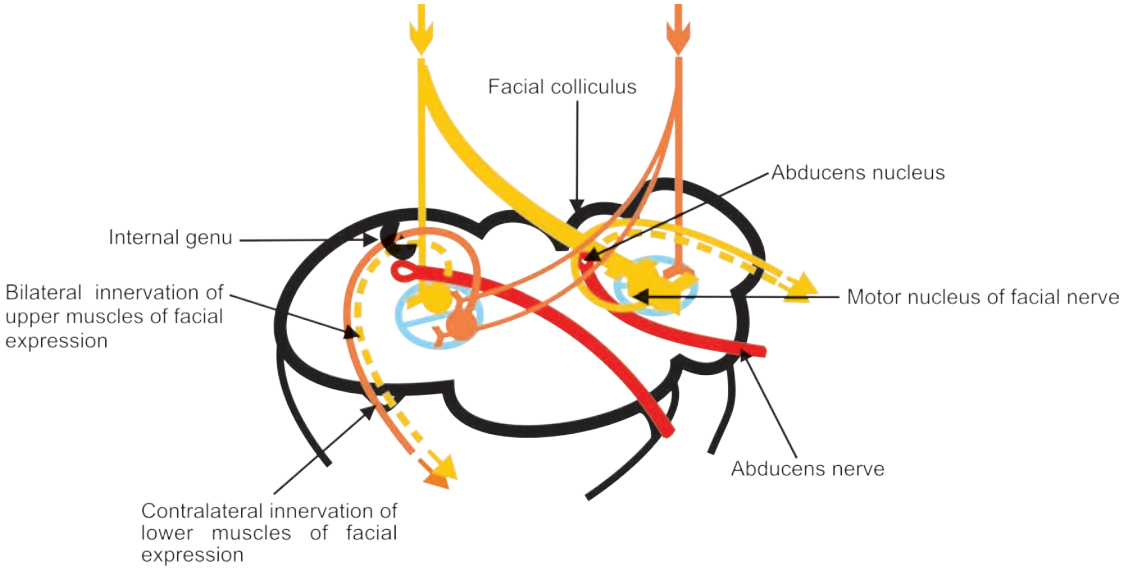

Fig. 12.14: Facial motor nucleus in the pons

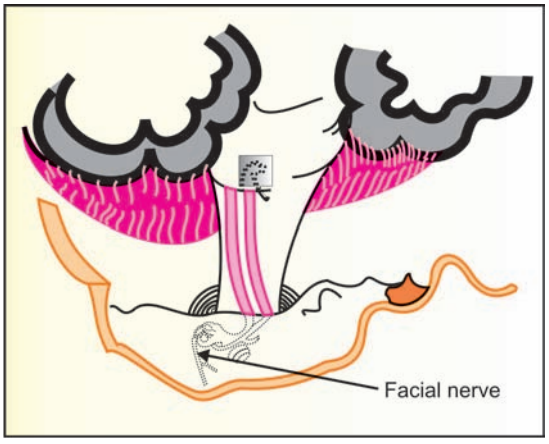

Fig. 12.15: Course of facial nerve in facial canal

The tympanic segment (horizontal segment) of facial nerve runs backwards in relation to the medial wall of the middle ear and turns gradually (pyramidal turn) to continue downwards as mastoid segment (vertical segment) along the junction of medial wall and posterior wall of the middle ear to give off the nerve to stapedius. The remaining branchial motor fibers reach the stylomastoid foramen.

After emerging from the stylomastoid foramen it gives off the stylohyoid nerve, nerve to posterior belly of digastric, and posterior auricular nerve to innervate the occipitalis muscle. The facial nerve then pierces and lies within the substance the parotid gland. At this point the facial nerve divides into five branches (Fig.12.16) which are as follows:

Component	Muscles innervated
Branchial motor	Stapedius
	Stylohyoid
	Posterior belly of digastric
	Muscles of facial expression
	Buccinator
	Platysma
	Occipitalis

Fig. 12.16: Muscles innervated by branchial motor component of facial nerve

1. Temporal branch
2. Zygomatic branch
3. Buccal branch
4. Mandibular branch
5. Cervical branch

Upper Motor Neuron Lesion (UMNL)

Damage to any part of the upper motor neuron in the cortex results in upper motor neuron lesion (Fig.12.17). Voluntary control of lower muscles of facial expression is lost contralateral to the lesion. Upper muscles of facial expression continue to function, because the part of the facial nucleus that innervates them still receives input from the ipsilateral cortex. The most common upper motor neuron lesion that involves facial nerve is cerebrovascular accident that damages the upper motor neurons in the cortex.

Lower Motor Neuron Lesion (LMNL)

Damage to any part of the lower motor neuron anywhere along its course results in lower motor neuron lesion (Fig.12.18). All the muscles of facial expression (upper and lower) innervated by the lower motor neurons are paralyzed ipsilateral to the lesion. Bell's palsy is a lower motor neuron lesion.

Bell's Palsy

Bell's palsy was named after the British neurosurgeon, neuroanatomist and artist, Sir Charles Bell (Fig.12.19). As his services were required during the "Battle of Waterloo" he got a unique opportunity to study the anatomy and musculature of the face as a result of facial gunshot injuries. Battlefield experiences combined with animal experiments done in his laboratory led to his conclusion that the seventh cranial nerve controlled facial expression. He named the seventh cranial nerve "the respiratory nerve of the face" and described its functions.

"*In all the exhilarating emotions, the eyebrows, eyelids, the nostrils and angle of the mouth are raised. In the depressing passions it is reverse.*"

His contributions to the medical field were rewarded with a knighthood in 1831, by King George IV. Some speculate that the enigmatic and curious smile of Mona Lisa (la Giaconda) might be the result of Bell's palsy. Careful examination of her portrait reveals a subtle asymmetrical smile—perhaps a clue about her medical history (Fig.12.20).

Bell's palsy is a common and cosmetically devastating cranial neuropathy. It accounts for about half of all cases of paralysis affecting the face. Bell's palsy is defined as an idiopathic, unilateral, lower motor neuron facial paresis (partial loss of movement), or paralysis (complete loss of movement) of acute onset in which no other etiology, such as infection, neoplasm or trauma, can be identified. Incidence of Bell's palsy is approximately 15 to 40 cases per 100,000 people per year, with a recurrence rate up to 10%.

Etiology

Since, by definition Bell's palsy is idiopathic; its exact cause is unknown. However, recent studies suggest that HSV-1 may play a role. PCR assays have identified HSV-1 in the endoneurial fluid and saliva in patients with Bell's palsy.

Therefore, idiopathic Bell's palsy may actually be a reactivation of the latent HSV-1 in the geniculate ganglion. Reactivation of the latent HSV-1 may in response to stress, fever, dental extraction, menstruation, or immunosupression.

Reactivation of HSV-1 causes acute inflammation and edema of the facial nerve in the narrow facial canal especially at the meatal foramen. Acute inflammation and edema of the facial nerve, leads to compression ischemia and conduction block of nerve signal. Due to conduction block of nerve signal, all actions of the facial muscles are affected, and there is atrophy of the facial muscles. This results in marked facial asymmetry.

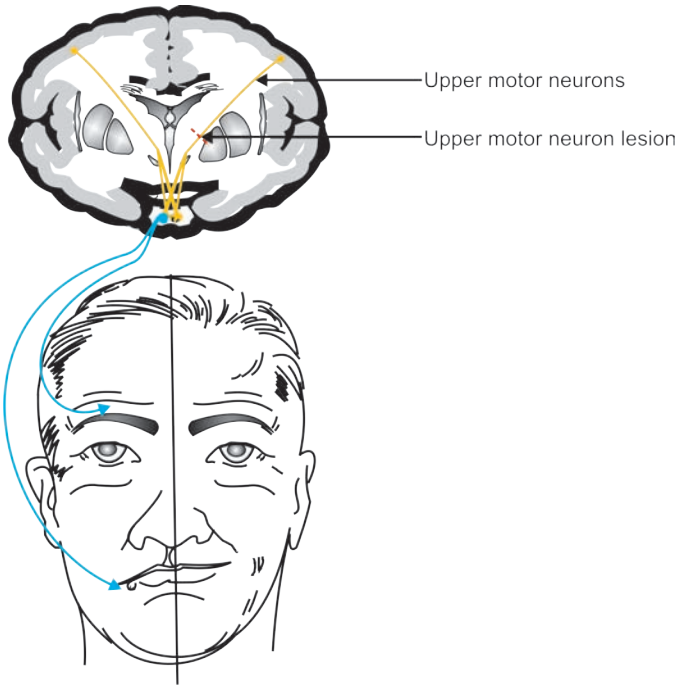

Fig. 12.17: Upper motor neuron lesion

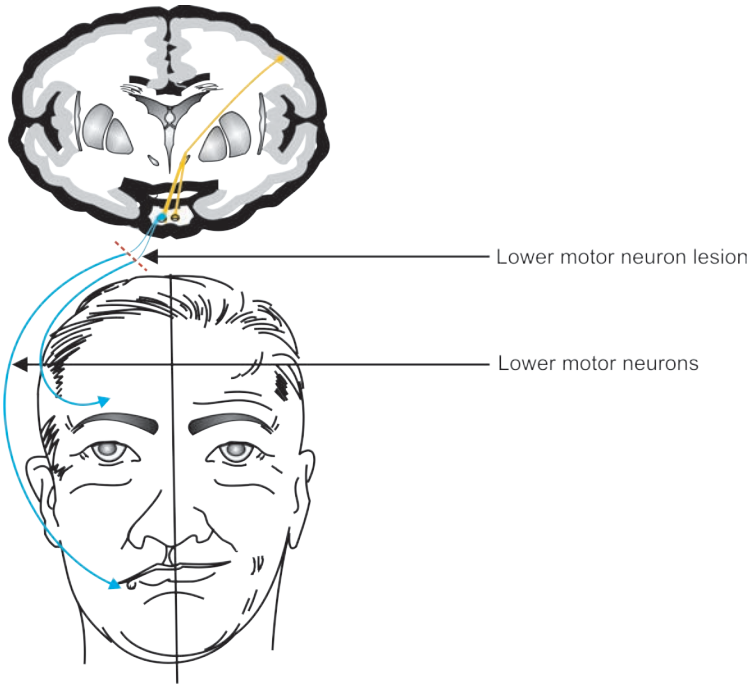

Fig. 12.18: Lower motor neuron lesion

Fig. 12.19: Sir Charles Bell (1774-1842)

Fig. 12.20: Mona Lisa

Clinical Features

Age: Most cases occur among people between 40-44 years, but it can affect all age groups, including children. Incidences of Bell's palsy are (Fig.12.21):

1. Lowest in children under 10 years
2. Increases from the ages of 10 to 29
3. Remains stable at the ages of 30 to 69
4. Highest in people over the age of 70

Sex: Men and women are equally affected i.e., with no gender bias.

Anatomical location: The left and right sides of the face are involved with equal frequency. In less than 1% of all cases, Bell's palsy may affect both sides of the face at once. Bilateral facial palsy (diplegia) should remind of Mobius syndrome, and myasthenia gravis.

Genetics: About 10% of patients with Bell's palsy have a family history.

Predisposing factors: Those at high risk include pregnant women and people with diabetes mellitus. Most often in the third trimester of pregnancy, the risk of Bell's palsy increases by 3:3 times, especially with concurrent pre-eclampsia. Pre-eclampsia is an abnormal state of pregnancy characterized by hypertension, fluid retention and albuminuria, which can lead to eclampsia if untreated. Eclampsia is characterized by convulsions and possibly coma during or immediately after pregnancy.

Clinical Presentation (Fig.12.22 and 12.23A and B)

1. Sudden pain especially below the ear probably due to neuritis of the facial nerve in the mastoid segment
2. Abrupt onset with complete, unilateral facial weakness at 24 to 72 hours
3. Facial asymmetry
4. Loss of wrinkling on forehead

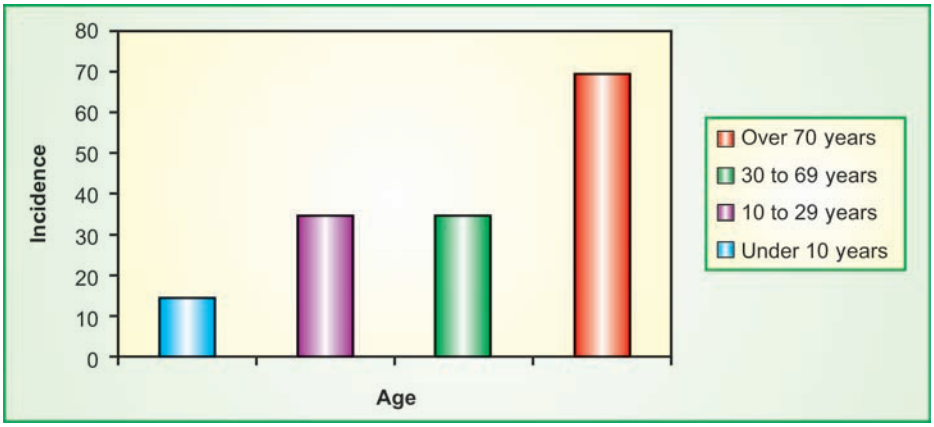

Fig. 12.21: Incidence of Bell's palsy

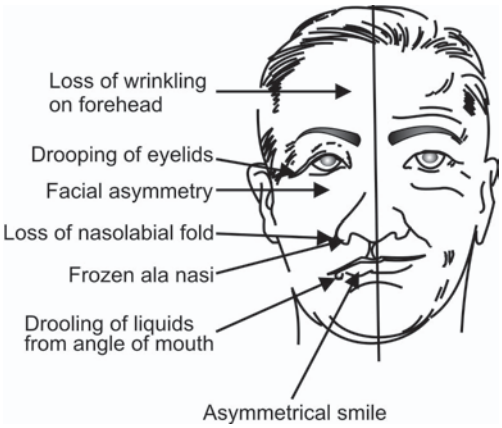

Fig. 12.22: Clinical presentation of Bell's palsy

5. Unable to elevate eyebrow
6. Drooping of the eyelid (ptosis)
7. Incomplete eyelid closure (lagophthalmos)
8. Flattened nasolabial fold
9. Frozen ala nasi
10. Asymmetrical smile
11. Difficulty in eating and speaking
12. Drooling of liquids from angle of mouth
13. Xerostomia and dryness of eyes is (present in 15 to 17% of patients) due to involvement of the visceral motor component
14. Ageusia on the lateral border of the anterior two-third of the tongue due to involvement of special sensory component. However,

Fig. 12. 23A: Facial asymmetry in patient with Bell's palsy of the left side of face

Fig. 12.23B: Bell' s phenomenon in patient with Bell's palsy of the left side of the face

there is no loss of general sensation as the tongue is innervated by the lingual branch of the mandibular nerve

15. The function of the stapedius muscle is to dampen the vibrations of the ear ossicles. Hyperacusis results from paralysis of the stapedius muscle, causing sounds to be abnormally loud on the affected side (hypersensitivity to sounds). There is no hearing loss
16. The practitioner should test for Bell's phenomenon. This is done by asking the patient to close his eyes. On the affected side the upper eyelid is pulled upwards, causing an upward movement of eyeball with only the scleral rim being exposed.

Prognosis

The spontaneous course of Bell's palsy includes: paresis or incomplete paralysis and complete paralysis. Majority of the patients with paresis have an excellent prognosis of recovery of facial nerve function without any sequelae (any abnormality resulting from a disease or injury or treatment) within a six-week period.

However, some patients who develop complete facial nerve paralysis show recovery of facial nerve function (House-Brackmann grade I and II) within three weeks. Patients with complete facial paralysis, who do not show any signs of recovery over three months after the onset of Bell's palsy, are left with various permanent sequelae (House-Brackmann grade III to V). These patients may benefit the most from medical or surgical treatment.

Electrodiagnostic Testing

The tests used to establish prognosis in Bell's palsy include the NET (nerve excitability test), MST (maximum stimulation test), ENoG (electroneurography), and EMG (electromyography).

With the first three days after the onset of facial palsy, electrical studies reveal no changes as Wallerian degeneration does not take place. The results during this time will be near normal. Because of this limitation, the prognosis cannot be established until 4th or 5th day. However, there is a steady decline in electrical activity from the 4th or 5th day onwards as Wallerian degeneration of damaged nerve fibers takes place. If there is 90% or greater reduction in the amplitude of ENoG waveform on the affected side, the prognosis worsens.

Sequelae

Sequelae of Bell's palsy are characterized as minor and major (Fig. 12.24).

1. **Aguesia:** Ageusia is defined as loss or absence of taste sensation
2. **Dysacusis:** Dysacusis is defined as difficulty in processing details of sound due to paresis of the stapedius muscle
3. **Epiphora:** Epiphora is defined as an overflow of tears upon the cheek, due to imperfect drainage by the tear-conducting passages
4. **Synkinesis:** During regeneration *(reproduction)* and reinnervation *(restoration of innnervation)*, some nerves grow along aberrant (different) pathways resulting in synkinesis. Synkinesis is defined as

Minor	Major
Ageusia	Residual paresis
Dysacusis	Tension
Epiphora	Contracture and tension
Gustatory lacrimation	Tics and spasms
Nasal obstruction	Synkinesis

Fig. 12.24: Minor and major sequelae of Bell's plasy

involuntary movement of facial muscles accompanying voluntary facial movement e.g., Many patients with Bell's palsy develop "jaw winking" which is closure of the eye when attempting to smile

5. **Gustatory lacrimation:** Crocodile tears syndrome, also called gustatory lacrimation, gustolacrimal reflex, paroxysmal lacrimation and Bogorad's syndrome. It is one of the rare complications of Bell's palsy and was described by a Russian neuropathologist in 1913. After Wallerian degeneration, regenerating preganglionic parasympathetic fibers of the chorda tympani (visceral motor component of facial nerve) that project to the submandibular ganglion may regrow (misdirected) through the greater petrosal foramen to stimulate the lacrimal gland secretion (lacrimal fluid) on the same side when the patient eats or drinks. The syndrome may also occur following acoustic neuroma surgery, maxillofacial trauma, and Paget's disease.

Differential Diagnosis

Bell's palsy is a common cause of facial nerve paralysis. Before making a diagnosis of Bell's palsy, other specific causes of facial nerve paralysis should be considered. The differential diagnosis of Bell's palsy is broad. Some of the common conditions that cause facial nerve paralysis include: Ramsay-Hunt syndrome, Lyme disease, malignancies of parotid gland, diabetes mellitus, and Melkersson-Rosenthal syndrome (Fig.12.25).

One of the most common causes of facial nerve paralysis is Ramsay-Hunt syndrome, or herpes zoster oticus, caused by the varicella zoster virus. Ramsay-Hunt syndrome is characterized by:

1. Vesicular lesions in the preauricular skin, external auditory canal, or the soft palate
2. Hearing loss
3. Ringing of the ears (tinnitus)
4. Vertigo due to extension of viral infection to involve vestibulocochlear nerve

Some of the other causes of facial nerve paralysis are (alphabetical order):

1. Acoustic neuroma
2. AIDS
3. Alcoholic neuropathy
4. Altitude paralysis (barotrauma)
5. Amyloidosis
6. Eosinophilic granuloma
7. Facial injuries
8. Forceps delivery
9. Hemangioma
10. Hypertension
11. Hyperthyroidism
12. Inferior alveolar nerve anesthesia
13. Leprosy
14. Malaria
15. Mastoiditis
16. Mobius syndrome (facial diplegia associated with other cranial nerve deficits)
17. Multiple sclerosis
18. Mumps
19. Paget's disease
20. Parotitis

Disease	Clinical presentation
Ramsay-Hunt syndrome	Vesicular lesions in the external auditory canal
Lyme disease	Exhibits a rash known as erythema chronicum migrans
Malignancies of parotid gland	Palpation of parotid gland will exhibit a hard mass
Diabtes mellitus	History of diabetes
Melkersson-Rosenthal syndrome	Unilateral facial palsy, facial edema, and lingua plicata (scrotal tongue)

Fig. 12.25: Common conditions causing facial nerve paralysis

21. Sarcoidosis
22. Scuba diving (barotrauma)
23. Syphilis
24. Tuberculosis
25. von Recklinghausen's disease

Diagnosis

Case history and physical examination provide information key to the diagnosis of Bell's palsy. Most patients do not require any laboratory testing or imaging studies. However, patient's who have persistent facial weakness without significant improvement, require further investigations. Diagnosis of Bell's palsy includes:

1. Case history and physical examination
2. Laboratory examination
3. Hearing testing
4. Imaging

Case History and Physical Examination

Physical examination helps rule out other conditions and narrow the differential diagnosis of Bell's palsy. Things to observe are:

1. ***Whether it is UMNL or LMNL?***
   Facial weakness is best demonstrated by the patient's response to the requests "*close your eyes" (for testing the upper facial area*) and "*show me your teeth* (*for testing the lower facial area*." In an UMNL, the patient is unable to close the eyes on the affected side due to denervation of the orbicularis oculi muscle. In an LMNL, the patient is unable to show the teeth and close the eyes on the affected side due to denervation of the risorius and orbicularis oculi muscles.
   a. Is Bell's phenomenon present?
   b. Assess the facial nerve damage using "House-Brackmann facial nerve grading system."

Laboratory Examination

Laboratory testing is necessary if the patient has signs of systemic disease, such as fever, weight loss, rash, or progressive facial weakness over more than 4 weeks. A number of tests may be helpful:

1. CBP and differential count–Leukemia
2. Blood glucose–Diabetes mellitus
3. Serum antibodies against VZV–Ramsay-Hunt syndrome
4. Serum antibodies against *Borrelia burgdoferi* –Lyme disease
5. Serum calcium and angiotensin-converting enzyme levels–Sarcoidosis

Hearing Testing

If hearing loss is suspected, then audiometry should be performed to measure hearing loss and to help rule out facial nerve tumors e.g., acoustic neuroma and involvement of vestibulocochlear nerve.

Imaging

Computed tomography (CT) or magnetic resonance imaging (MRI) is indicated in the following cases:

1. No improvement in facial paralysis after one month
2. Hearing loss
3. Multiple cranial nerve deficits
4. Signs of limb paresis or sensory loss

Treatment

Most patients with Bell's palsy recover completely and achieve normal function within a few months. Though treatment of Bell's palsy is still controversial, evidence suggests that oral steroids and antiviral medications shorten the disease course. However, there is only limited evidence to show that these treatments are effective. Surgical decompression of the facial nerve is controversial and should be considered for patients who have a poor clinical outcome.

Oral Steroids

Oral steroids have been shown to limit denervation *(to cut off the innervation)*, within the

first 24 hours or so after the onset of the symptoms. Oral steroids have been used to control the inflammation and edema which results in facial nerve entrapment. Patients treated with oral steroids have fewer incidents of synkinesis. The most commonly used oral steroid regimen is 10-day course of oral prednisolone (60 mg a day orally for 5 days, tapered by 10 mg a day for 5 days).

Antiviral Drugs

As the recent studies implicate HSV-1 as the likely cause of Bell's palsy, antiviral therapy should be added to the oral steroid regimen. The most commonly used antiviral regimen is 10-day course of oral acyclovir (400 mg orally five times daily). Combination therapy (oral prednisolone and oral acyclovir) improves the outcome of patients.

Ocular Management

Artificial tears and sunglasses should be used to prevent exposure keratitis of the cornea. Areas contaminated by excessive matter or noxious fumes (construction areas, textile factories) should be avoided. To protect cornea during sleep, an ophthalmic ointment should be used along with a crescentic piece of tape placed on the upper eyelid. A gold weight may be fitted into the upper eyelid to keep the eyelid closed (eyelid will still open normally). A surgical technique called tarsorrhaphy, which narrows the space between the eyelids, may improve eye closure.

Facial Exercise

Facial exercise can be beneficial in patients with Bell's palsy. They should be performed while standing in front of a mirror. Facial exercises include trying to raise the eyebrows, blowing, and whistling. These exercises can be performed a few times daily.

Recurrence

Bell's palsy rarely recurs. Approximately 7-12% of patients develop recurrent Bell's palsy. Usually the second attack affects the opposite side. Recurrence is more likely seen in patients with a family history, pregnancy, and in those with diabetes mellitus.

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Glossary

Abscess: A localized accumulation of pus or purulent material in a cavity formed by tissue disintegration, e.g., periapical abscess.

Acantholysis: Loss of cohesion between the cells in the spinous layer.

Acanthosis: Increased thickness of spinous layer or stratum Malphigii.

Active immunity: Protection from a disease as a result of previous exposure to the disease-causing infectious agent or antigen. The protection can be a result of having had the disease or having received a vaccine to prevent getting the disease.

Acute: Phenomenon characterized by a quick, fast course, as opposed to chronic.

Acute inflammation: A traumatic or pathologic phenomenon or process having a short and relatively severe course. In contrast to chronic inflammation, the host immune response quickly overwhelms the injurious agent, which is followed by the resolution of pathologic process and recovery or death of the patient.

Acupuncture: A Chinese medical treatment involving the insertion of very fine sterile needles into the body at specific points according to a mapping of "energy pathways."

Abrasion: It is the pathologic wearing away of the tooth substance due to abnormal mechanical process and usually occurs on the exposed root surfaces of the teeth (cervical region). Frequently caused by abrasive dentrifice, improper brushing technique, improper use of dental floss and tooth picks (interproximal abrasion), and habitual opening of bobby pins (incisal abrasion).

Administration: How a drug or therapy is introduced into the body. Systemic administration means that the drug goes throughout the body (usually carried in the bloodstream), and includes oral (by mouth), intravenous or parenteral (injection into the vein, IV), intralesional (injection into the lesion), intramuscular (injection into a muscle, IM), intraarticular (injection within the joint space), intrathecal (injection into the spinal canal), subcutaneous (injection beneath the skin, SQ), and rectal administrations. Local administration means that the drug is applied or introduced into the specific area affected by the disease, such as application directly onto the affected skin surface (topical administration). The effects of most therapies depend upon the ability of the drug to reach the affected area; thus the route of administration and consequent distribution of a drug in the body are important determinants of its effectiveness.

Adverse reaction: An unwanted effect caused by the administration of drugs. Onset may be sudden or develop over time.

Adenopathy: Any disease involving or causing enlargement of glandular tissues, especially one involving the lymph nodes.

Adjuvant: An ingredient added to a prescription or solution that facilitates or modifies the action of the principal ingredient.

Aerobes: Microorganisms that can live and grow in the presence of oxygen, e.g., *Mycobacterium tuberculosis.*

Agammaglobulinemia: A nearly total absence of immunoglobulin's resulting in the loss of ability to produce immune antibodies.

Agenesis: It is defined as failure of an organ to develop, e.g., anodontia due to agenesis of enamel organ.

Agonists: Drugs that can combine with receptors present on cell membrane to produce a physiological reaction.

Aguesia: Ageusia is defined as loss or absence of taste sensation.

AIDS: The most severe manifestation of infection with the Human Immunodeficiency Virus (HIV). The Centers for Disease Control and Prevention (CDC) lists numerous opportunistic infections and cancers that, in the presence of HIV infection, constitute an AIDS diagnosis. In 1993, CDC expanded the criteria for an AIDS diagnosis in adults and adolescents to include CD4+ T cell count at or below 200 cells per microliter in the presence of HIV infection. In persons (age 5 and older) with normally functioning immune systems, CD4+ T cell counts usually range from 500–1,500 cells per microliter. Persons living with AIDS often have infections of the lungs, brain, eyes, and other organs, and frequently suffer debilitating weight loss, diarrhea, and a type of cancer called Kaposi's sarcoma.

AIDS wasting syndrome: The involuntary weight loss of 10 percent of baseline body weight plus either chronic diarrhea (two loose stools per day for more than 30 days) or chronic weakness and documented fever (for 30 days or more, intermittent or constant) in the absence of a concurrent illness or condition other than HIV infection that would explain the findings.

Allergen: A substance capable of producing an allergic response. Common allergens are pollens, dust, drugs or foods.

Allergy: A hypersensitive reaction (antigen-antibody reaction) of the body to an allergen.

Allodynia: Pain without noxious stimuli.

Alopecia: Loss of hair that frequently occurs in patients undergoing chemotherapy for cancer or suffering from other diseases, such as AIDS, where cell-killing or cytotoxic drugs are used.

Ambidextrous: Able to use either hand (right or left) equally well e.g., ambidextrous latex gloves.

Amino acid: Amino acids are the building blocks of proteins.

Anachoresis: The accumulation of particulate material or microorganisms from the circulating blood in certain sites in the tissues.

Anaerobes: Microorganisms that can live and grow in partial or complete absence of oxygen, e.g., *Bacteroides forsythus*.

Analgesia: Absence of sensibility to pain.

Anaphylactic shock: A life-threatening allergic reaction characterized by a swelling of body tissues (including the throat) and a sudden decline in blood pressure. Symptoms include difficulty breathing, violent coughing, and chest constriction.

Anaplasia: When the normal cells undergo differentiation to resemble embryonic tissue.

Anemia: Anemia is a term indicating that the concentration of hemoglobin or the number of red blood cells is below the accepted normal value with respect to age and sex.

Anesthesia: Absence of all sensation.

Angiogenesis: The process of forming new blood vessels. Angiogenesis is essential for the growth of tumors, especially Kaposi's sarcoma.

Anorexia: The lack or loss of appetite that leads to significant decline in weight.

Antagonists: Drugs that neutralizes or counteracts the effects of another drug.

Antenatal: Occurring before birth.

Antibiotic: A natural or synthetic substance that inhibits the growth of microorganisms such as bacteria or fungi. Some antibiotics are used to treat infectious diseases.

Antibodies: Protein formed and secreted by B cells derived plasma cells to an antigenic stimulus.

Antifungal: A substance that kills or inhibits the growth of a fungus.

Antigen: A protein that often stimulates the production of antibodies.

Antigen presentation: The event of providing fragments of foreign proteins, including viruses and bacteria, to the helper CD4+ and CD8+ T cells.

Antigen presenting cell (APCs): APCs are the cells, which process the antigen and present it to the T cell receptor present on CD4+ T cells in combination with MHC class II molecules or CD8+ T cells in combination with MHC class I molecules. Examples of APCs are macrophages, B cells, and Langerhans cells (dendritic cells).

Antioxidants: Agents that inhibits oxidation and thus prevents the deterioration of other materials through oxidative processes.

Antiviral: A substance that kills or inhibits the growth of a virion.

Anxiety Mental disorder characterized by increased muscle tension, perspiration, movements of hand and feet. He/She frequently seeks assurance and asks number of questions.

Apical periodontitis: Inflammation of the periodontal ligament at the apical region of the tooth, as sequelae of pulpitis.

Apical scar: A radiolucent area at the periapex of a tooth characterized histologically by dense fibrous connective tissue.

Aplasia: When the hypoplasia is very severe it is called aplasia, e.g., aplastic anemia.

Apoptosis: Derived from Greek meaning "dropping off," this means programmed cell death occurring in normal tissues or pathologic tissues.

Artery: A blood vessel through which the blood passes from the heart to the various structures of the body.

Arterioles: A minute arterial branch proximal to a capillary.

Arthralgia: Pain in a joint or joints.

Arthritis: Inflammation of joint or joints.

Artifact: Tissue that has been altered physically from its natural state by processing.

Asepsis: Without infection or free of viable pathogenic microorganisms.

Ataxia: Lack of muscular coordination.

Attrition: It is the pathologic wearing away of the occlusal surface of tooth as a result of tooth-to-tooth contact. Frequent causes are bruxism, and chewing tobacco.

Atrophy: It is defined as decreased in size of an organ or tissue due to decrease in number of cells, e.g., atrophic epithelium in oral sub mucous fibrosis.

Autoantibodies: Antibodies produced against one's own antigens.

Autoimmunity: Autoimmunity is a condition in which there is immune response to one's own tissues. Most of the vesiculo-bullous diseases are autoimmune. Autoimmune diseases have a female predilection, increased serum autoantibodies, and hypergammaglobulinemia.

Avulsion: The sudden tearing out of tissue as a result of trauma e.g., avulsion of a tooth.

Bacteremia: The presence of viable bacteria in the blood.

Bacteria: Single-celled spherical (coccus), spiral (spirillum), rod-shaped (bacillus), comma-shaped (vibrio), and corkscrew-shaped (spirochete) organisms lacking chlorophyll that reproduce by fission; important as pathogens and for biochemical properties.

Bactericidal: Capable of killing bacteria.

Bacteriostatic: Capable of inhibiting reproduction of bacteria.

B lymphocytes: A short-lived, nonthymus dependent form of lymphocytes that synthesize antibodies. They are the precursors of plasma cells.

Basophil: A type of granulocyte, which has coarse granules and a bent lobed nucleus found in the blood and resembles the tissue mast cell.

bid: Twice a day dosing instructions.

Biopsy: Surgical removal of pathologic tissue from a living being for histopathological examination.

Blister: Common term used for vesicle or bulla.

Blood: A red colored fluid circulating through the heart, arteries, capillaries, and veins and carries nutrients and oxygen to body tissues.

Blood clot: A coagulum formed of blood of a semisolidified nature.

Blood pressure: The lateral pressure exerted on the arterial walls by the blood.

Bone marrow: Soft tissue located in the cavities of the bones where blood cells such as erythrocytes, leukocytes, and platelets are formed.

Brachy: Meaning short.

Brachycephalic: Broad, round head.

Brachychilia: Abnormally short lips.

Brachyglossal: Abnormally short tongue.

Brachytherapy (internal radiation therapy): Brachytherapy uses radiation that is placed very close to or inside the tumor. The radiation source is usually sealed in a small holder called an implant. Implants may be in the form of thin wires, plastic tubes called catheters, ribbons, capsules, or seeds. The implant is put directly into the body. Internal radiation therapy may require a hospital stay. is usually delivered in one of two ways: interstitial radiation therapy and intracavitary or intraluminal radiation therapy.

Bronchoconstriction: The reduction in the caliber of the bronchi.

Bronchodilation: The increase in the caliber of a bronchus.

Bronchodilator: A drug that dilates or expands the diameter of the bronchi by relaxing the muscular walls.

Bronchospasm: A spasmodic contraction of the muscular walls of the bronchi.

Bulla: Elevated, fluid-filled blister measuring greater than 0.5 cm in diameter, e.g., mucous membrane pemphigoid.

Calculus: A concretion composed of calcium phosphate, calcium carbonate, magnesium phosphate, and other elements within an organic matrix composed of desquamated epithelial cells, mucin, microorganisms, and other debris.

Cancer: The word cancer was coined by Hippocrates. In Latin, cancer means "Cancrum" denoting crab.

Cancerophobia: Fear of cancer.

Cachexia: General ill health and malnutrition, marked by weakness and emaciation, usually associated with serious disease.

Capillaries: The terminal vessels uniting the arterial with the venous systems of the body.

Carcinoma: A malignant tumor arising from epithelial cells, e.g., squamous cell carcinoma.

Carcinogen: Any cancer-producing substance.

Case history: A detailed and concise compilation of all demographic, personal, medical, physical, and dental factors relative to diagnosis, prognosis and treatment.

Causalgia: Post-extraction localized pain, usually characterized by a continuous burning sensation.

CD4: Cell surface glycoprotein usually on helper T cells.

CD8: Cell surface glycoprotein usually on cytotoxic T cells.

Central lesion: A pathology present within the bone causing enlargement, loss of function and loss of continuity.

Cell: According to the cell, doctrine cells are the fundamental units of both structure and function in all living things.

Cellulitis: A diffuse red, tender inflammatory process that spreads along fascial planes and through tissue spaces without gross suppuration.

Chemotaxis: A response involving movement that is positive (toward) or negative (away) to a chemical stimulus e.g., phagocytic activity of neutrophils and monocytes.

Chemotherapy: In general, it is the use of medications to treat cancer.

Chemoprophylaxis: The use of a drug or chemical to prevent a disease.

Chief complaint: This is the reason, usually a symptom or cluster of symptoms, why the patient seeks treatment.

Chronic: Phenomenon characterized by a long, slow course, as opposed to acute.

Chronic inflammation: A traumatic or pathologic phenomenon or process, which is a slow, insidious, event that persists for several months to years. Chronic inflammation results when the injuring agent persists in the lesion, and the host's immunity responds in a manner that is not sufficient to overcome the effects of the injurious agent.

Chromosomes: Darkly staining bodies present in the nucleus that are observed in cells during division. Each chromosome carries genes in a linear order.

Civatte bodies: Apoptotic cells.

Clade: Also called a subtype. A clade is a group of related HIV isolates classified according to their degree of genetic similarity (such as the percentage of identity within their envelope genes).

Clinical: Pertaining to or founded on observation and treatment of patients, as distinguished from theoretical or basic science.

Clinical latency: The period of time a virus or bacteria or other organism is living or developing in the body without causing symptoms.

Cloacae: Penetration of involucrum by channels (cloacae) through which pus escapes to an epithelial surface.

Clubbing (pulmonary osteoarthropathy): Deforming enlargement of the terminal phalanges of the fingers. It is usually acquired and may be associated with certain cardiac and pulmonary diseases.

Collagen: Derived from a Greek word meaning to produce glue. Collagen is the most abundant protein, which is found in skin, tendons, ligaments, muscles, teeth (dentine), and mucosa.

Corticosteroids: Compounds that resemble cholesterol chemically and also contain hydrogenated cyclopentanoperhydrophenanthrene ring system e.g., hydrocortisone secreted by adrenal corticosteroids. Endoge-nously cortisone is probably a metabolite of hydrocortisone. When exogenous cortisone is given, it exhibits no biological activity until it is converted to hydrocortisone (cortisol).

Combination therapy: Two or more drugs or treatments used together to achieve optimum results against a disease e.g., AIDS.

Complement: A group of serum proteins involved in inflammation, phagocytosis, and cell lysis.

Concomitant drugs: Drugs that are taken together.

Connective tissue (lamina propria): The binding and supportive tissue of the body; derived from the mesoderm and is composed of fibroblasts, primitive mesenchymal cells, collagen fibers, elastic fibers with associated blood vessels, lymphatic vessels, and nerve fibres embedded in a ground substance.

Convulsion: A violent spasm.

Crepitus (coarse): Coarse grating noise suggestive of gross bone-on-bone contact.

Crepitus (fine): Fine grating noise suggestive of mild bone-on-bone contact.

Crust: Desiccated contents of ruptured vesicle.

Cryotherapy: The use of liquid nitrogen to freeze and destroy a lesion or growth, sometimes used to induce scar formation and healing to prevent further spread of a condition.

Cyanosis: A characteristic bluish tinge or color of the skin and mucous membranes associated with reduction in hemoglobin brought about by inadequate respiratory change.

Cyst: "A cyst is a pathological cavity having fluid, semi fluid or gaseous contents and which is not created by the accumulation of pus" (Kramer, 1974).

Cytotoxic T lymphocyte: CD8+ T cells which kill target cells.

Cytokines: Low molecular weight proteins that stimulate or inhibit the differentiation, proliferation, or function of immune cells.

Cytotoxic: An agent or process that is toxic or destructive to cells.

Data gathering: Comprehensive collection of information about the patient through case history and examination.

Definitive (final diagnosis): Diagnosis derived after using differential diagnosis is the definitive or final diagnosis.

Dental caries: An infectious disease of the tooth with progressive destruction of tooth substance, beginning on the external surface by demineralization of enamel or exposed cementum.

Dementia: Chronic intellectual impairment (i.e., loss of mental capacity) with organic origins that affects a person's ability to function in a social or occupational setting.

Demyelination: Destruction, removal, or loss of the myelin sheath of a nerve or nerves.

de novo: Arising anew, afresh, once more, from the beginning.

Depression: Mental disorder characterized by gloominess, sadness, lack of motivation and interest.

Desensitization: Gradually increasing the dose of a medicine in order to overcome severe reactions.

Desmoplasia: Formation and development of fibrous tissue.

Desmosome: Structure that attaches cells, especially in stratified squamous epithelium of the skin and mucosa.

Dolichocephalic: Long and narrow head.

Drug-drug interaction: A modification of the effect of a drug when administered with another drug. The effect may be an increase or a decrease in the action of either substance, or it may be an adverse effect that is not normally associated with either drug.

Diagnose: To make a diagnosis.

Diagnosis: Diagnosis is an assessment of the clinical findings, which may help in identifying a specific disease.

Diagnostic: Relating to or aiding in diagnosis.

Diagnostician: One who is experienced in making diagnosis.

Diapedesis: The passage of blood or any of its formed elements (cells), through the intact walls of the blood vessels.

Differential diagnosis: It is a process of identifying a specific disease from other diseases that may produce similar signs and symptoms.

Diffusion: The random movement of free molecules or ions or small particles in solution or suspension under the influence of Brownian (thermal) motion toward a uniform distribution throughout the available volume.

Diplegia (double hemiplegia): Paralysis of corresponding parts on both sides of the body.

DNA: Deoxyribonucleic acid is the genetic material of the cells and many viruses, e.g., Herpes simplex virus-1.

Drug: A substance used in the prevention, cure, or alleviation of pain or disease.

Drug resistance: The ability of some disease causing microorganisms, such as bacteria, viruses, and fungi, to adapt themselves, to multiply, and to grow even in the presence of drugs that usually kill them.

Dys: Prefix which means bad or difficult.

Dysacusis: Impairment in the sense of hearing (difficulty in processing details of sound).

Dysaphia: Impairment in the sense of touch.

Dysesthesia: Impairment of sensation short of anesthesia (unpleasant sensation).

Dysguesia: Impairment in the sense of taste.

Dysphagia: Difficulty in swallowing.

Dysphasia: Lack of coordination in speech.

Dysplasia: Abnormal tissue development e.g., epithelial dysplasia in precancerous lesions.

Dyspnea: Difficult or labored breathing.

Dystrophy: It is defined as a congenital disorder of the structure or function of an organ or tissue e.g., craniocarpotarsal dystrophy (ulnar deviation of hands, frontal bone defects, protrusion of lips, sunken eyes with hypertelorism) or muscular dystrophy (congenital abnormality of muscle associated with dysfunction and ultimately deterioration).

Ecchymosis: Discoloration of mucous membrane caused by diffuse extravasations of blood. Frequently called a bruise.

Ectoderm: The outermost layer of the embryo. The ectoderm gives rise to the nervous system, the organs of the special senses, the epidermis, and epidermal tissues such as fingernails, hair and sebaceous glands.

Embolus: A blood clot, mass of bacteria, or other foreign body that travels in the blood vessels and then deposits in a vessel to obstruct circulation.

Endoderm: The innermost layer of the embryo. The endoderm gives rise to the epithelial lining of the primitive gut tract, its glands, and the epithelial component of structures arising from the gut.

Endogenous: Relating to or produced by the body.

Endotoxin: A toxin present inside a bacterial cell.

Eosinophils: A leukocyte that has coarse granules, which contain toxic cationic proteins.

Epidemic: A disease that spreads rapidly through a demographic segment of the human population, such as everyone in a given geographic area. Epidemic diseases can be spread from person to person or from a contaminated source such as food or water.

Epidemiology: The branch of medical science that deals with the study of incidence and distribution and control of a disease in a population.

Epiphora: Epiphora is defined as an overflow of tears upon the cheek, due to imperfect drainage by the tear-conducting passages.

Epistaxis: Bleeding from the nose.

Erosion: It is the loss of tooth substance caused by chemical process that does not involve bacteria and usually involves the palatal aspect of upper anterior teeth. Frequent causes are anorexia nervosa, simple vomiting, hyperemesis gravidarum (chronic vomiting in pregnant women), and consumption of acidic fruit beverages malic acid (apples), tartaric acid (grapes), and citric acid (citrus fruits).

Erosion: Partial loss of the epithelium without the exposure of underlying connective tissue e.g., erosive lichen planus or pathologic loss of tooth substance seen on the palatal surface of maxillary anteriors due to chemicals and involving bacteria.

Erythema: Redness or inflammation of the skin or mucous membranes.

Erythrocyte sedimentation rate: The rate at which red blood cells of unclotted blood settle in a pipette, measured in millimeters per hour. It is used as an index for infection.

Erythroplakia: Oral erythroplakia is a predominantly red lesion of the oral mucosa that cannot be characterized as any other definable lesion.

Etiology: The study or theory of the factors that cause disease.

Exogenous: Developed or originating outside the body.

Exophthalmos: An abnormal protrusion of the eyeball, it is characteristic of toxic (exophthalmic) goiter.

Exotoxin: A toxic substance, made by bacteria released outside the bacterial cell.

Extravasation: The escape of a body fluid out of its proper place e.g., extravasation of blood into the surrounding tissues after trauma.

Exudate: A tissue fluid that has high protein content in comparison to transudate.

Fascicle: A bundle.

Fibroblast: Connective tissue cell that produces collagen and plays an important role in wound healing.

Fibrosis: The process of forming fibrous tissue e.g., oral submucous fibrosis.

Final diagnosis: The diagnosis arrived after collecting, analyzing, and subjecting the data to logical thought.

Fistula: Abnormal tract connecting two cavities and may or may not be lined by epithelium, e.g., oro-antral fistula.

Fixative: Any substance used to preserve gross or histological specimens of tissue for later examination e.g., 10 % neutral buffered formalin.

Follicle: A small anatomical sac, cavity, or deep narrow mouthed depression e.g., hair follicle.

Fracture: Break of a part. In the oral and maxillo-facial region, fracture is most frequently seen in teeth and bones.

Fulguration: The destruction of soft tissue by an electric spark that jumps the gap from an electrode tip to the soft tissue without the electrode tip touching the tissue e.g., fulguration artifact in LASER biopsy.

Fungus: A plantlike organism feeding on organic matter, such as mushrooms, yeasts (*Candida albicans*), and molds.

Gangrene: The death of a tissue en masse, usually as a result of loss of blood supply, bacterial invasion, and subsequent putrefaction e.g., gangrene of the pulp is total death and necrosis of the pulp.

Ganglion: A mass of nervous tissue composed principally of nerve-cell bodies, usually lying outside the central nervous system.

Gene: A unit of DNA that carries information for the biosynthesis of a specific product in the cell. Genes are arranged along the length of, the chromosome. Alteration of either gene number or arrangement can result in mutation.

Genome: The complete set of genes in the chromosomes of each cell of a particular organism.

Gene therapy: Any experimental treatment in which cell genes are altered.

Genetic engineering: The technique by which genetic material from one organism is inserted into a foreign cell in order to produce the protein encoded by the inserted genes.

Giant cell: An abnormally large tissue cell. It often contains more than one nucleus and may appear as a merger of several normal cells e.g., Langhans' giant cell, Tzanck cells, Touton giant cell, Foreign body giant cell, Reed-Sternberg giant cells, Anitschkow cells, giant cell, Syncytia of CD4+ T cells in HIV, gigantoblast (abnormally large erythroblast), gigantocyte (abnormally large erythrocyte).

Gingivitis: Inflammation of the gingiva.

Glossodynia: When the symptoms of the burning mouth are limited to the tongue the term glossodynia is preferred.

Gluconeogenesis: The formation of blood glucose from proteins.

Glycogenesis: The formation of liver and muscle glycogen from blood glucose.

Glycogenolysis: The formation of blood glucose from liver and muscle glycogen.

Glycoprotein: A conjugated protein in which the nonprotein group is a carbohydrate (i.e., a sugar molecule) also called glucoprotein.

Gram-positive: Microorganisms that appear violet colour after being stained with Gram's stain.

Gram-negative: Microorganisms that appear rose pink after being stained with Gram's stain.

Granuloma: Localized mass of granulation tissue characterized by an accumulation of giant cells, epithelioid cells, macrophages and lymphocytes, e.g., tuberculosis.

Granulation tissue: Pink tissue formed during the wound healing process, mainly composed of proliferating capillaries and plump fibroblasts. Overgrowth of granulation tissue is called "Proud Flesh".

Growth: An increase in size.

Ground substance: The ground substance supports the connective tissue and its various elements (see connective tissue) and consists of protein-carbohydrate complexes, which are permeable to tissue fluid. Chemically the protein-carbohydrate complexes can be subdivided into two distinct groups, proteoglycans, and glycoproteins. The proteoglycans consist of long polypeptide chain to which numerous hexose and hyaluronic acid residues are attached. The hyaluronic acid residues are responsible for the water binding capacity of the connective tissue. In comparison, the glycoproteins consist of branched polypeptide chain to which only a few simple hexoses are attached.

Haematoma: Collection of a mass of extravasated blood in the tissues due to rupture of blood vessels because of trauma; usually bluish-purple in colour.

Hamartomata: Tumor like malformations of oral tissues, developmental in origin, with the tissue being native to the site, e.g., odontoma (complex and compound), dens invaginatus, dens evaginatus, talon's cusp, enameloma, hemangioma, lymphangioma, glomus tumor, torus palatinus, torus mandibularis, pigmented cellular nevus, Epstein's pearls, and oral melanotic macule.

Half-life: The time required for half the amount of a drug to be eliminated from the body.

Headache (cephalagia, cerebralgia, cephalodyia): Diffuse pain in various parts of the head resulting from intracranial, extracranial and psychogenic causes.

Hematotoxic: Poisonous to the blood or bone marrow.

Hemidesmosome: Structure that attaches basal cells of the stratified squamous epithelium of the skin and mucosa with the basal lamina.

Hemiplegia: Paralysis of one side of the body.

Hemoglobin: The component of red blood cells that carries oxygen.

Hemolysis: The rupture of red blood cells.

Hemorrhage: Excessive bleeding or loss of large amount of blood from the blood vessels within a short period of time.

Helper T cell: CD4+ T cells responsible for cell–mediated immunity.

Histological basis of red lesions:

1. Atrophy of epithelium
2. Increased blood supply
3. Dilated blood vessels
4. Hemorrhage

Histological basis of white lesions:

1. Increased thickness of epithelium
2. Development of surface fungal colonies (*Candida albicans*)
3. Decreased blood supply
4. Increased keratin production

HLA: Human leukocyte antigens (HLA) are a series of proteins and their genes are located at a number of loci along the short arm of chromosome 6. The main loci are designated A, B, C, DR (D-related). HLA antigens are detectable on the surface of most nucleated cells e.g., basal cell layer of the epithelium.

Hormone: Chemical messengers secreted into the blood vessel from ductless glands (endocrine

glands). The hormone (e.g., growth hormone) is formed in one gland (e.g., pituitary gland) and carried in the blood vessel to another tissue (e.g., bone) where it influences cellular activity, especially growth and metabolism.

Hyalin: A clear, eosinophilic, homogenous substance occuring in degeneration e.g., juxta-epithelial hyalinization of lamina propria in OSF.

Hyaline: Glassy, homogenous, translucent appearance. The term refers to characteristic gross and microscopic appearance and not a specific chemical substance.

Hyalinization: The formation of hyalin.

Hyaluronic acid: A mucopolysaccharide made up of alternating residues of glucuronic acid and N-acetylglucosamine, forming a gelatinous material in connective tissue spaces, and as an intercellular cementing substance.

Hyperalgia: An increased sensitivity to pain that may result from a pain stimulus or decreased pain threshold.

Hyperacusis: Hypersensitivity to normal environmental sounds.

Hypercalcemia: An increase in the amount of calcium in the blood. Causes include primary hyperparathyroidism, sarcoidosis, multiple myeloma, malignant neoplasms, prolonged androgen therapy, and massive doses of vitamin D.

Hypercapnia: An increase in the amount of carbon dioxide in the blood resulting from increase of carbon dioxide in the inspired air or a decrease in elimination.

Hypercementosis: An excessive formation of cementum on the root/roots of one or more teeth.

Hyperesthesia: Increased sensitivity to stimulation.

Hyperemia: An increase in the amount of blood in a tissue. The hyperemia can be active (increased blood flow due to dilatation of arterioles and capillaries) or passive (decreased outflow of the blood from a tissue e.g., physical obstruction or pressure from a tumor).

Hyperglycemia: An increase in the concentration of sugar in the blood and is a feature of diabetes mellitus.

Hyperkalemia: An increase in the amount of potassium in the blood. Causes include advanced dehydration, shock, renal failure, and Addison's disease.

Hypernatremia: An increase in the amount of sodium in the blood. Causes include nephrosis, congestive cardiac failure, after administration of ACTH, and Cushing's syndrome.

Hyperostosis: Excessive growth of bone as in infantile cortical hyperostosis.

Hyperpigmentation: An unusual darkening of the skin. Causes include heredity, exposure to sun, drugs, pregnancy, and endocrinal disturbances.

Hyperplasia: Increase in size of an organ or tissue due to increase in number of its cells, e.g., fibroma arising from the gingiva.

Hypersalivation (sialorrhea, ptyalism): Increased secretion of saliva. Causes include acute stomatitis, ill-fitting dentures, pregnancy, teething, alcoholism, malnutrition, mental retardation, neurological disorders, and cystic fibrosis.

Hypersensitivity (allergy): Abnormal or excessive sensitivity to an antigen. The hypersensitivity reactions are traditionally subdivided into four types, three are antibody mediated injuries (Type I, Type II, Type III), whereas the fourth is cell mediated (Type IV).

Hypertelorism: Increased distance between paired organs as in Greig's (ocular hypertelorism) syndrome.

Hypertension: Abnormal elevation of systolic and/or diastolic arterial pressure.

Hypertrichosis: Excessive growth of hair on the body e.g., hirsutism due to excessive adrenocortical function.

Hypertrophy: Increase in size of an organ or tissue due to increase in size of its cells, e.g., hypertrophy in muscles due to mechanical stimulus.

Hypervolemia: Increased blood volume.

Hypoalgesia: A decreased sensitivity to pain that results from an increased pain threshold.

Hypocalcemia: A decrease in the amount of calcium in the blood e.g., hypoparathyroidism, rickets, osteomalacia.

Hypocapnia: A decrease in the amount of carbon dioxide in the blood.

Hypoesthesia: Decreased sensitivity to stimulation.

Hypoguesia: Decreased sense of taste.

Hypoglycemia: A decrease in the concentration of sugar in the blood. Common causes include fasting, and following injection of insulin.

Hypokalemia: A decrease in the amount of potassium in the blood. Hypokalemia may occur in chronic diarrhea, metabolic acidosis, Cushing's syndrome, excessive use of ACTH, and primary aldosteronism.

Hyponatremia: A decrease in the amount of sodium in the blood. Hyponatremia may develop in extreme sweating, chronic renal failure, and adrenocortical insufficiency.

Hypoplasia: Condition in which there is small under developed organ.

Hyposalivation (xerostomia): Dryness of the mouth (decreased or absence of saliva) resulting from functional or organic disturbances of the salivary glands.

Hypotension: Low systolic and/or diastolic arterial pressure.

Hypotrichosis: A less than normal amount of hair on the body.

Hyperkeratosis: Condition characterized by hyperkeratinization of keratinized mucosa.

Hypoesthesia: Decreased sensitivity to stimulation.

Hypoxia: Reduction of oxygen supply to tissues.

Hypothesis: A supposition or assumption advanced as a basis for reasoning or argument, or as a guide to experimental investigation.

Icterus (jaundice): A condition characterized by an abnormal accumulation of bilirubin in the blood and manifested by the yellowish discoloration of the skin, mucous membranes, and skin.

Idiopathic: Without a known cause.

Immunity: A natural or acquired resistance to a specific disease. Immunity may be partial or complete, long lasting, or temporary.

Immune complex: Clusters formed when antigens and antibodies bind together.

Immune deficiency: Breakdown in immunocompetence, when certain parts of the immune system no longer function. This condition makes a person more susceptible to certain diseases.

Immune response: The activity of the immune system against foreign substances.

Immune system: The body's complicated natural defense against disruption caused by invading foreign agents (e.g., microbes, viruses). There are two aspects of the immune system's response to disease: innate and acquired. The innate part of the response is mobilized very quickly in response to infection and does not depend on recognizing specific proteins or antigens foreign to an individual's normal tissue. It includes complements, macrophages, dendritic cells, and granulocytes. The acquired, or learned, immune response arises when dendritic cells and macrophages present pieces of antigen to lymphocytes, which are genetically programmed to recognize very specific amino acid sequences. The ultimate result is the creation of cloned populations of antibody-producing B cells and cytotoxic T lymphocytes primed to respond to a unique pathogen.

Immunocompetent: 1. Capable of developing an immune response. 2. Possessing a normal immune system.

Immunocompromised: Refers to an immune system in which the ability to resist or fight off infections and tumors is subnormal.

Immunofluorescence: The use of fluorescein–labeled antibodies to identify bacterial, viral, or other antigenic material specific for the labeled antibody. Immunofluorescence tests are either direct or indirect.

Immunotherapy: Treatment aimed at reconstituting an impaired immune system.

Incidence: The number of new cases (e.g., of a disease) occurring in a given population over a certain period of time.

Incompetence: Incompetence is defined as defective closure of the cardiac valve e.g., defective closure of the aortic valve permitting backward flow of blood into the left ventricle during ventricular diastole.

Induration: Abnormal hardening of soft tissue because of influx of exudate or fibrous tissue elements.

Inflammation: Body's reaction to injury and is characterized by five cardinal signs namely rubor, calor, tumor, dolor, and functio laesa.

Infarct: An infarct is an area of necrotic tissue that has died because of lack of oxygenated blood.

Infarction: The death of a tissue caused by partial occlusion of a vessel or vessels supplying the area.

Infection: An invasion of tissues by disease producing microorganisms and the reaction of these tissues to the microorganisms and/or their toxins. The mere presence of microorganisms without reaction is not an evidence of infection.

Innervation: The supply of nerve fibers.

In situ: From the Latin, meaning in the original place.

In vitro: From the Latin, meaning "within the glass"; an artificial environment created outside a living organism (e.g., a test tube or culture plate) used in experimental research to study a disease or process.

In vivo: From the Latin, meaning "within the living organism"; studies conducted within living organisms (e.g., animal or human studies).

Ionizing radiation: Radiation which causes removal of orbital electrons from atoms in the irradiated matter and converting those atoms to electrically charged atoms or free radicals e.g., X-rays.

Ischemia: A focal deficiency of blood to a part of the body (in simple terms a local anemia). It results from impingement of the lumen of a blood vessel supplying the affected area. Causes of impingement are allergic hypersensitivity, atherosclerosis, inflammation, physical pressure, pharmacological or toxic agents, and neurogenic disorders.

Keratosis: Condition characterized by hyperkeratinization of nonkeratinized mucosa.

Ketogenesis: The formation of ketone bodies from adipose tissue.

LASER: "Laser" is an acronym for "light amplification by simulated emission of radiation." Basically, a laser beam is generated when an external power source stimulates a chamber containing laser medium-solid, liquid or gas.

Lesion: A general term to describe an area of altered tissue (e.g., the infected patch or sore in a skin disease).

Leukemia: Progressive proliferation of abnormal leukocytes found in hemopoietic tissues, other organs, and usually in the blood in abnormal numbers.

Leukoplakia: Oral leukoplakia is a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion.

Locus: Position of a gene on the chromosome.

Lower motor neuron: Neuron located in the brain stem is lower motor neuron. Its cell bodies are located in brain stem and axons leave this

nucleus makes up the motor component of cranial nerves.

Luxation: Dislocation or displacement of a tooth from the socket or the temporomandibular joint from the articular fossa.

Lymph: Lymph is a clear watery fluid, which originates in organs and tissues of the body. It is similar in composition to plasma, with the exception of plasma proteins. Lymph transports the plasma proteins that seep out of the capillary bed back to the blood vessels. It also carries away bacteria and cell debris from damaged tissues, which can then be filtered out and destroyed in the lymph nodes.

Lymphadenitis: An inflammation of a lymph node or nodes characterized by swelling, pain, and redness.

Lymphadenopathy: Enlargement (localized or generalized) of a lymph node or nodes resulting from a disease.

Lymphatics: The lymphatic system consists of a series of lymph vessels, which begin as blind-end tubes in the spaces between the blood capillaries and tissue cells. The lymphatic system consists of lymph capillaries, thin lymph vessels, large lymph vessels. The large lymph vessels eventually join together to form 2 large ducts, the thoracic duct and right lymphatic duct, which empty the lymph into the subclavian veins.

Lymphoma: Neoplasm made up of lymphoid tissue e.g., B cell lymphoma, T cell lymphoma, Burkitt lymphoma, non-Hodgkin lymphoma, Hodgkin lymphoma.

Lymphokines: Cytokine produced by lymphocytes.

Lymph nodes: Lymph nodes are small oval or bean-shaped organs of the immune system, which lie in groups, along the length of lymph vessels.

Macrophages: Any phagocytic cell of the reticuloendothelial system including specialized Kupffer's cells in the liver and spleen, and histocytes in loose connective tissue.

Macule: Flat circumscribed discolored nonelevated area of oral mucosa or skin.

Malaise: A generalized, nonspecific feeling of discomfort.

Manometer: An instrument used to indicate pressure of gases or vapor, or the tension of the blood.

Manometry: Measurement of pressure of gases or vapor, or the tension of the blood by means of manometer.

Macroglossia: Abnormally large tongue.

Mast cells: A connective tissue cells whose specific physiological function remains unknown; capable of elaborating (expanding) basophilic, metachromatic, cytoplasmic granules that contain histamine.

Meiosis: It is a special process of cell division that produces four reproductive cells in sexually reproducing organisms; the nucleus divides into four nuclei each containing half the chromosome number leading to gametes (ova and sperm) in animals and spores in plants).

Mesocephalic: Head size between dolichocephalic and brachycephalic.

Mesoderm: The middle of the three cell layers of the developing embryo. It lies between the ectoderm and endoderm. The mesoderm gives rise to bone, connective tissue, muscle, blood, vascular and lymphatic tissue, the pleurae of the pericardium and peritoneum.

Metaplasia: Condition in which the cells/tissue undergoes differentiation to another type of similar cells/tissue e.g., stratified squamous epithelium undergoing metaplasia to pseudostratified columnar epithelium, mucous cells, and sebaceous cells in dentigerous cyst.

Metastasis: The spread of a disease (e.g., cancer) from an original site to other sites in the body.

MHC (major histocompatibility complex): A genetic region encoding proteins involved in antigen presentation to T cells. Class I MHC molecules are present on virtually all nucleated cells and are encoded mainly by the HLA-A, B,

and C in man while Class II MHC molecules are expressed on APC (primarily macrophages, B cells, Langerhans cells) and are encoded by HLA-DR, DQ, and DP in man.

Migraine: A vascular type of headache, typically unilateral in the temporal, frontal, and retroorbital area, but may occur in the midfacial region. It is described as throbbing, burning, pulsating, exploding, or pressure and may become generalized and persist for hours or days. Onset of pain is usually preceded by prodromal symptoms that may include visual disturbances, nausea, and vomiting.

Mitosis: Division of the cell that produces two daughter cells exactly like the parent cell.

Morbidity: The relative incidence of a particular disease.

Mortality: The ratio of deaths in an area to the population of that area; expressed per 1000 per year.

Mucosa: A membrane composed of epithelium and lamina propria that lines the oral cavity and other canals and cavities of the body that communicate with external air.

Mucous: The viscous, slippery secretions of mucous membranes and glands, containing mucin, white blood cells, water, inorganic salts, and exfoliated cells.

Mutagen (carcinogen): An environmental agent, physical, chemical or biological, that is capable of inducing mutations.

Mutation: The process by which a mutagen produces an alteration in DNA or chromosome.

Myalgia: Pain felt in the muscles.

Myopathy: Progressive muscle weakness.

Necrosis: The local death of cell or group of cells resulting from, loss of blood supply, bacterial toxins, or physical and chemical agents. Examples include caseous (tuberculosis), exanthematous (noma), gingival (ANUG), ischemic (trauma of the pulp), and radiation.

Nausea: A sensation of leading to the urge to vomit.

Neonatal: Concerning the first 6 weeks of life after birth.

Neoplasm (tumor): "A neoplasm is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissue and persists in the same excessive manner after cessation of the stimuli which evoked the change (Sir Rupert Willis).

Neuralgia: Neurogenous pain that is felt along the pathway of peripheral nerve.

Neurosis: Mental disorder characterized by inability to cope with frustrations and is milder than psychosis.

Neutrophils: The major circulating phagocytic polymorphonuclear granular leukocyte. Enters tissues early in an inflammatory response and is also able to mediate (in-between) antibody-dependent cellular cytotoxicity.

Nodule: Solid lesion located within the subcutaneous tissue.

Non-reproducible click: Present on opening or in laterotrusion but not repeatable.

NK (natural killer) cells: Large granular lymphocyte which does not rearrange nor express either immunoglobulin or T cell receptor genes but is able to recognize and destroy certain tumor and virally infected cells in an MHC and antibody-independent manner.

NSAID: A classification of drugs called nonsteroidal anti-inflammatory drugs. NSAIDs reduce inflammation and are used to treat arthritis and mild to moderate pain.

od: Once a day dosing instructions.

Odontalgia: Pain felt in the tooth.

Oncogene: Oncogenes are mutated forms of genes that cause normal cells to grow out of control and become cancer cells or a gene that causes cancer.

Oral cancer: Malignancy that arises from oral tissues, e.g., squamous cell carcinoma.

Oral medicine: The "*American Academy of Oral Medicine*" defines oral medicine as follows: Oral Medicine is the specialty of dentistry concerned with the oral health care of medically complex patients and with the diagnosis and non-surgical management of medically-related disorders or conditions affecting the oral and maxillofacial region.

Organ: Any part of the body exercising a specific function e.g., respiration, digestion.

Orthokeratosis: Keratinization in which nuclei are not present.

Osmosis: The net diffusion of water across a selectively permeable membrane from a region of high water concentration (low solute concentration) to a region that has low water concentration (high solute concentration) until the concentration on both sides is equal.

Osteomyelitis: Inflammation of the medullary portion of the bone.

Palliative: A treatment that provides symptomatic relief but not a cure.

Pallor: Paleness. Absence of skin or mucous membrane.

Paresthesia: Abnormal sensation.

Pandemic: A disease prevalent throughout an entire country, continent, or the whole world.

Parakeratinization: Keratinization in which nuclei are present.

Passive immunity: Also referred to as acquired immunity. Resistance resulting from previous exposure to an infectious agent or antigen may be active or passive. Passive immunity can be acquired from the transfer of antibodies from another person or from an animal, either naturally—as from mother to fetus or to the newborn via breast milk—or by intentional inoculation (vaccination).

Pathogen: Any disease-producing microorganism or material.

Palsy: Paresis or paralysis.

Paralysis: Impairment of motor function due to trauma or lesion of the neuron or muscles e.g., facial paralysis.

Paresis: Partial or incomplete paralysis.

Pain: Unpleasant sensation created by a noxious stimulus, which is mediated along a specific nerve pathway to the central nervous system where it is interpreted as such.

Papule: Raised circumscribed discolored elevated area of mucosa or skin, which is less than 1 cm in diameter, e.g., stomatitis nicotina.

Pathogenesis: The origin and development of a disease.

Peduncle: A constricted portion (stalk or stem), forming the attachment of a nonsessile tumor.

Perinatal: Events that occur at or around the time of birth.

Periapical abscess: An acute or chronic inflammation of the periapical tissues characte-rized by a localized accumulation of pus at the apex of a tooth. It is generally a sequela of pulp death of tooth.

Periapical granuloma: Mass of granulation tissue surrounded by fibrous capsule, which is attached to the root.

Periodontitis: Inflammation of the periodontium (teeth, gingiva, cementum of the root, periodontal ligament) and alveolar bone or alterations occuring in the periodontium with inflammation.

Peripheral lesion: Pathology present within the soft issue causing enlargement, loss of function and loss of continuity.

Peripheral resistance: Peripheral resistance is the resistance offered by the arterioles to blood flow. Thus, the arterioles are called resistance vessels. In the body, the maximum peripheral resistance is offered at the splanchnic region.

Petechiae: Capillary hemorrhages producing small red or purplish pin head-sized discolorations of the mucosa membrane and skin.

Plaque: Elevated flat-topped area, usually more than 5 mm across.

Plasma: The liquid part of the blood and lymph that contains nutrients, electrolytes (dissolved salts), gases, albumin, clotting factors, wastes, and hormones.

Plasma cell: Terminally differentiated B lymphocyte which actively secretes large amounts of antibody.

Polyp: Mass of a tissue that bulges outwards or upwards from the normal mucosa or skin, which is either pedunculated or sessile.

Polydipsia: Abnormally increased thirst.

Polyuria: The passage of an abnormally increased volume of urine. It may result from increased intake of fluids, inadequate renal function, uncontrolled diabetes mellitus or diabetes insipidus, and ascites.

Polyphagia: Abnormally excessive eating.

Popping: Distinctly audible sound on opening.

Precancerous condition: Generalized state associated with a significantly increased risk for cancer.

Precancerous lesion: Morphologically altered tissue, in which cancer is more likely to occur than in its apparently normal counterpart.

Prevalence: A measure of the proportion of people in a population affected with a particular disease at a given time.

Prodrome: A symptom that indicates the onset of a disease.

Prophylaxis: Treatment to prevent the onset of a particular disease ("primary" prophylaxis), or the recurrence of symptoms in an existing infection that has been brought under control ("secondary" prophylaxis, maintenance therapy).

Proto-oncogene: A gene that has a high rate of transforming into oncogene.

Provisional diagnosis: Diagnosis which is not final or fully worked out or agreed upon.

Pruritis: Itching.

Psychosis: Personality disorder characterized by hallucinations/delusions.

Psychasthenia: Mental disorder characterized by abnormal reaction to environment.

Pulpitis: Inflammation of the pulpal tissue of a tooth.

Purpura (bruise): A discoloration of mucous membrane caused by diffuse extravasation of blood.

Pustule: Vesicle containing pus rather than clear fluid.

Putrefaction (decomposition): The breakdown of organic matter usually by bacterial action, resulting in the formation of other substances of less complex constitution and malodorous products (e.g., ammonia and hydrogen sulfide ("rotten egg smell").

Pyrexia: Elevation of body temperature.

qid: Four times a day dosing instructions.

Radiotherapy (actinotherapy, irradiation, radiation therapy, X-ray therapy,): The speciality of medicine which relates to the use of X-rays to kill cancer cells and shrink tumors. Radiation therapy injures or destroys cells in the area being treated (the "target tissue") by damaging their genetic material, making it impossible for these cells to continue to grow and divide. Although radiation damages both cancer cells and normal cells, most normal cells can recover from the effects of radiation and function properly. The goal of radiation therapy is to damage as many cancer cells as possible, while limiting harm to nearby healthy tissue.

Reciprocal click: Noise made on opening and closing from centric occlusion position that is reproducible on every opening and closing. Can be eliminated with anterior repositioning of jaw.

Red lesion: Abnormal area of oral mucosa that appears red is of a different texture than the adjacent normal mucosa, e.g., erythroplakia.

Referred pain: Pain felt at an area that is innervated by a nerve, which does not mediate the primary pain.

Regurgitation: Backflow of blood through a defective heart valve.

Reproducible closing click: Noise with every closing, no noise when opening.

Reproducible laterotrusive click only: Noise with every full laterotrusive movement, no noise on opening.

Reproducible opening click: Noise with every opening, no noise when closing.

Rheumatoid factor: IgM, IgG, IgA autoantibodies to IgG, particularly the Fc region.

Rhizotomy: Destruction of sensory root and ganglion.

RNA: Ribonucleic acid is the genetic material in certain microorganisms and is involved in transcription and translation (protein synthesis).

Saliva: The clear, slightly acid mucoserous secretion formed in the exocrine glands namely partotid glands (serous fluid), sublingual glands (mucous fluid), submandibular glands (serous and mucous fluid), and smaller intraoral salivary glands.

Sarcoma: Malignant tumor arising from connective tissue cells.

Scale: Dry, horny, plate like excrescence; usually the result of imperfect cornification (keratinization) or surface accumulation of desquamated epithelial cells.

Scar: The end product of wound healing.

Sepsis: The presence of harmful microorganisms or associated toxins in the blood.

Sequestrum: A piece of small necrotic bone that has become separated from vital bone. These small fragments of necrotic bone may be lysed completely, whereas larger ones are isolated by a bead of granulation tissue encased in a sheath of new bone (involucrum).

Serum: The clear, thin, and sticky fluid portion of the blood that remains after coagulation (clotting). Serum contains no blood cells, platelets or fibrinogen.

Seroconversion: The development of antibodies to a particular antigen.

Sessile: Having a broad base of attachment in comparison to pedunculated.

Sepsis: The presence of harmful microorganisms or associated toxins in the blood.

Shock: A sudden physical or mental disturbance e.g., anaphylactic shock, anesthetic shock, cardiogenic shock, electric shock, hemorrhagic shock, hypovolemic shock, irreversible shock, septic shock.

Side effects: The actions or effects of a drug (or vaccine) other than those desired.

Signs: Objective evidence of a disease, e.g., redness, ulcer, swelling, tenderness to palpation, tenderness to percussion, bad breath, molar crossbite.

Sinusitis: Inflammation of the nasal cavity and sinuses.

Sinus: Blind tract, which connects a cavity, from either the bone or soft tissue, to the epithelial surface, which is formed by granulation tissue and may or may not be lined by epithelium.

SOAP: Acronym often seen in medical and dental case histories, describes a routine approach to any disease and stands for: **S**ubjective symptoms, **O**bjective signs, **A**ssessment of clinical findings, and **P**lan i.e., treatment plan.

Spasm: A sudden involuntary contraction of a muscle or muscle group.

Sphygmo: (Greek for "*sphygmos*", pulse) Relating to pulse.

Sphygmomanometer: Instrument used to measure blood pressure or a pressure gauge for measuring blood pressure.

Spot diagnosis: Diagnosis made quickly on the spot.

Stenosis: Stenosis is defined as pathological narrowing of the cardiac valve orifice e.g., narrowing of the aortic valve orifice.

Stethoscope: An instrument originally designed by Laennec for aid in hearing the respiratory and cardiac sounds in the chest; now modified in various ways and used in auscultation of any vascular or other sounds in the body anywhere.

Stereo: Designating sound transmission from two sources through two channels.

Stereotactic surgery: A precise method of destroying deep-seated brain structures, located by the use of three-dimensional coordinates.

Subclinical infection: An infection, or phase of infection, without readily apparent symptoms or signs of disease.

Suppurative: Producing pus or associated with the formation of pus.

Swelling: It is an increase in size of a tissue caused by the exudation of fluid from the capillary vessels into the tissue spaces e.g., cellulitis.

Syncope: Temporary loss of consciousness or fainting due to decreased blood supply to the brain.

Syndrome: Group of signs and symptoms that occur together and characterize a disease.

Symptoms: Subjective evidence of a disease or sensation experienced by the patient indicative of a disease, e.g., pain, sensitivity to hot or cold, altered taste, inability to open the mouth.

Systemic: Concerning or affecting the body as a whole.

Subluxation: Incomplete dislocation of a joint e.g., TMJ subluxation.

Teratogenicity: Teratogenicity refers to capacity of a drug to cause fetal abnormalities when administered to the pregnant mother.

Teratomata: Tumor like malformation, which is not native to the site. The common sites are the ovary and testis e.g., testicular teratomata, ovarian teratomata (they are usually cystic, and the wall is lined by stratified squamous epithelium and contains sebaceous glands and hair follicles. The cystic cavity is usually lined by a greasy mass of sebaceous material in which there is matted hair. There is often a nodule in the wall, called "umbo", which contains a variety of structures such as bone, teeth, thyroid tissue, brain etc.

Teletherapy (external beam therapy): Teletherapy is a method for delivering a beam of high-energy X-rays to the location of the patient's tumor. The beam is generated outside the patient (usually by a linear accelerator and is targeted at the tumor site. These X-rays can destroy the cancer cells and careful treatment planning allows the surrounding normal tissues to be spared. No radioactive sources are placed inside the patient's body.

Therapy: Treatment of a disease e.g., antibiotic therapy, corticosteroid therapy, periodontal therapy, radiation therapy, root canal therapy, speech therapy.

Thrombocytopenia: Abnormal hematological condition in which the platelet count is reduced.

Thrombolus: An embolus composed of aggregated platelets.

Thrombus: A blood clot in a vessel or in one of the chambers of the heart that remains at its place of origin.

tid: Thrice a day dosing instructions.

Tissue: An aggregation of similarly specialized cells, which are united to perform particular function e.g., connective tissue (binding and supportive tissue of the body).

Translocation: Attachment of a fragment of one chromosome to another chromosome. The short arm of the chromosome is designated as p and the long arm q.

Trauma: External violence producing bodily injury or degeneration.

Trigger point: Trigger points are tender areas in firm bands of skeletal muscles, tendons, or ligaments.

Trigger zones: Junction between the two nerve endings where the nerve impulse is normally not transmitted (no synapse) is known as ephapse. However, when there is ephaptic transmission (short-circuit) between nociceptive afferents and non-nociceptive afferents it results in a trigger zone.

Trismus: Spasms of the muscles of mastication resulting in the inability to open the mouth e.g., pericoronitis.

Tumor suppressor gene: Tumor suppressor genes are normal genes that activate genes that promote DNA repair, activate genes that arrest cell division, and activate genes that promote apoptosis.

Tzanck cell: A degenerated epithelial cell caused by acantholysis, which is usually found in pemphigus.

Ulcer: Total loss of epithelium with exposure of underlying connective tissue, e.g., traumatic ulcer or aphthous ulcer.

Upper motor neuron: The neuron located in the cerebral cortex and which whose axon projects caudally to contact the lower motor neuron in the brain stem.

Vaccine: A substance that contains antigenic components from an infectious micro-organism. By stimulating an immune response it protects against subsequent infection by that organism. There can be preventive vaccines (e.g., measles or mumps) as well as therapeutic (treatment) vaccines.

Vasoconstriction: Narrowing of blood vessels.

Vasodilatation: Dilatation of blood vessels.

Vegetations: A clot composed blood platelets, fibrin, and bacteria adherent to the heart valve.

Veins: Veins are known as capacitance vessels because they can store large amounts of blood especially the splanchnic veins. Therefore, the sympathetic nerves richly supply the splanchnic veins. Thus, when there is venoconstriction; blood is pumped to important organs. The terms venoconstriction and venodilation are generally used to refer to constriction and dilation of capacitance vessels (veins).

Venules: The smallest of the venous blood vessels.

Vertical transmission: A term used to describe the transmission of a disease from parent or parents to offspring.

Vesicle: Elevated fluid-filled blister measuring less than a 0.5 cm in diameter.

Viral load (VL): The amount of HIV RNA in a blood sample, reported as number of HIV RNA copies per ml of blood plasma. The VL provides information about the number of cells infected with HIV and is an important indicator of HIV progression and how well the treatment is working. The VL can be measured by different techniques, including branched chain DNA (bDNA) and reverse transcriptase-polymerase chain reaction (RT-PCR) assays. VL tests are usually done when an individual is diagnosed with HIV infection and at regular intervals after diagnosis.

Viremia: The presence of virus in the bloodstream.

Viricide: Any substance that can destroy or inactivate a virus.

Virion: A virus particle existing freely outside a host cell. A mature virus.

Virulence: The power of a microorganism to produce disease.

Vitamins: Group of unrelated organic substances that occurs in small amounts in food and is required in normal metabolic activities and lack of which in the diet causes deficiency diseases. The vitamins may be water soluble or fat soluble.

von Recklinghausen's disease (neurofibromatosis, neuromatosis, molluscum fibrosum): Disease characterized by development of small discrete, pigmented skin lesions (café-au-lait spots) that develop in infancy or early childhood, followed by development of multiple

subcutaneous neurofibromas that many slowly increase in size and number over many years. Neurofibromas may develop on nerve trunks anywhere.

von Recklinghausen's disease of bone (hyperparathyroidism, generalized osteitis fibrosa cystica, brown tumor): Disease characterized by an increase in the secretion of paratharmone causing elevated serum calcium, and decreased serum phosphorus. It may be primary, secondary or tertiary.

Wheal: It is a special form of circumscribed papule produced by edema of epidermis and dermis.

Wheezing: A whistling sound made during breathing that is caused by a foreign body (mucus) in the bronchi or trachea.

White lesion: Abnormal area of oral mucosa that appears white and is of a different texture than the adjacent normal mucosa.

Window period: The window period is the time between initial infection with HIV and the development of enough antibodies to be detected through testing.

Working diagnosis (provisional diagnosis or tentative diagnosis): Diagnosis made when the clinical presentation corresponds to a particular disease, so that preliminary treatment may proceed.

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